

# Inhaled Steroids in Childhood Asthma

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# Alternative Titles

- How to classify asthma as persistent?
- Should all persistent asthma be treated with ICS?
- When and how to use alternative or add on medications?
- Can persistent asthma be treated intermittently?
- What are the risks?

# Why Bother?

- Prevalence: 8.9% of children, 7.2% of adults
- 6.5 million children (1.4 million < 5 years of age)
- Exacerbation rate: 5.2%/12 months (3.9% for adults)
- ED visits: 103/10,000 children (50/10,000 adults)
- Hosp rates: 27/10,000 children (14/10,000 adults)
- < 5 years old: 168 ED visits & 60 hosp/10,000

# How We Think About Asthma

- NAEPP Guidelines 2007
  - Severity
  - Control
  - Responsiveness

# How To Classify Severity

- Impairment Domain: Frequency and intensity of symptoms and functional limitations
- Risk Domain: Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects of treatment.

# Persistent Asthma: mild, moderate or severe

- Symptoms > 2 days/week to throughout the day
- Nighttime awakenings 2/month or more
- SABA use > 2 days/week to multiple times/day
- Any interference with normal activity
- Lung function may be normal at rest or abnormal
- Exacerbations 2 or more/year, esp if ED or hosp

# Goals of Treatment

- Prevent chronic and troublesome symptoms
- Infrequent use and need for rescue medication
- Maintain normal lung function
- Normal activity level
- Meet expectations and satisfaction with care
- Minimal or no side effects of treatment

# Goals 2

- Prevent exacerbations, ED visits, urgent care visits and hospitalizations (this is where the big cost is)
- Prevent progressive loss of lung function (prevent reduced lung growth in children) (prevent airway remodeling)

# How to Achieve the goals

- Control (prevent) asthma symptoms
- Control inflammation in the airways
- Reverse (prevent) airflow obstruction
- Improve quality of life (day and night)
- Decrease number and severity of exacerbations

# Sounds Like a Job for Superman!

- Inhaled corticosteroids are the only class of drugs shown to fit all of those criteria.
- But nothing has been shown to achieve the goal of preventing airway remodeling if it is going to occur.

# How do they work?

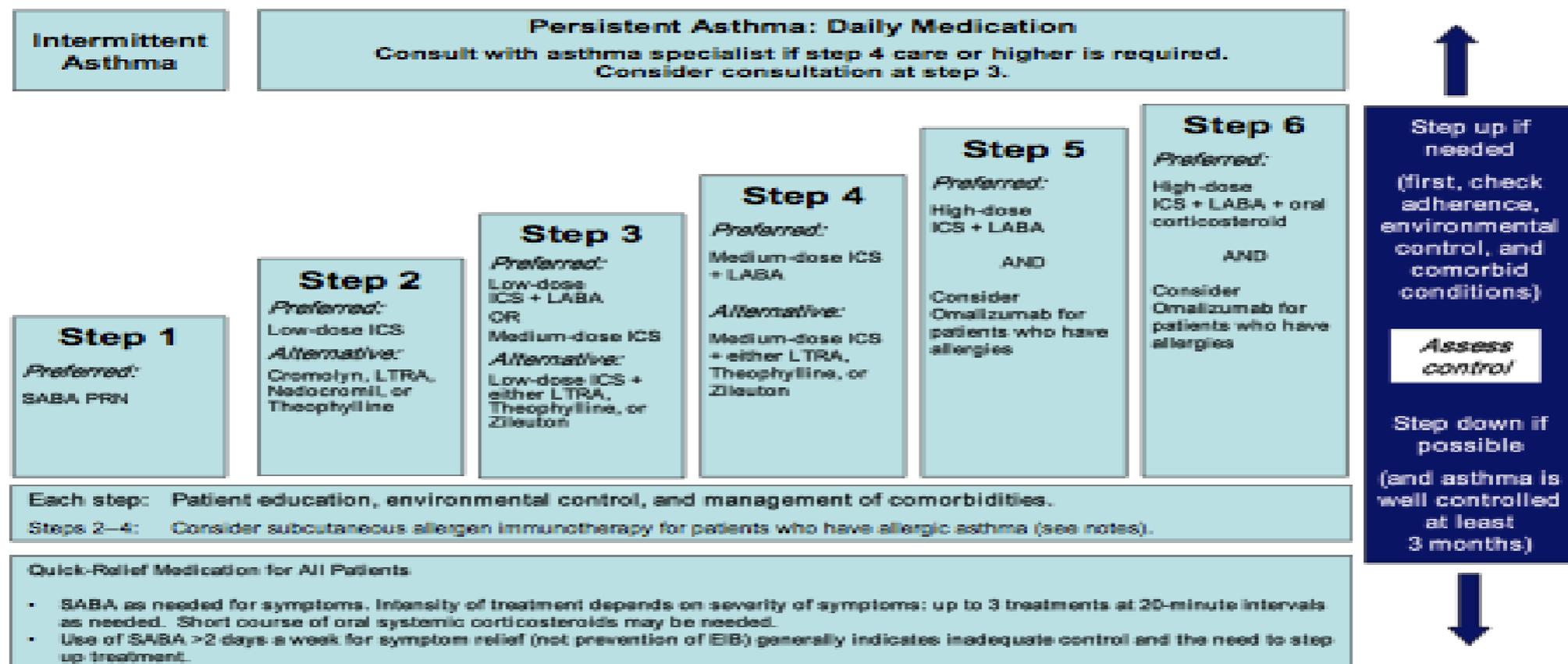
- Steroids work on multiple sites of the inflammatory reaction.
- Inhibit migration and activation of eosinophils & T-lymphocytes
- Block the late phase allergic reaction
- Block cytokines important in asthma: IL-4, IL-5, IL-9, IL-13, TNF- $\alpha$ , GM-CSF
- Decrease IgE & high affinity IgE receptors
- Decrease mediators: histamine, leukotriene, etc

# And all this leads to:

- Decrease in mucous hypersecretion
- Decrease airway smooth muscle hypertrophy
- Decrease airway hyperresponsiveness
- Decrease symptoms and severity of asthma
- But do they affect airway remodeling?

# Step-Care Approach

- Step 2-6 in the NAEPP guidelines recommend inhaled steroids as the first line treatment for all age groups
- Varies in dose and add-on drugs as go up the steps
- Alternatives only for step 2, the mildest persistent asthma
- All but the mildest patients should be in ICS

**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<sub>2</sub>-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist.

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

# Dosing ICS

- Most of the therapeutic effect of ICS occurs at low to medium doses
- High doses are occasionally necessary but usually add little
- Non linear dose-response curve
- But side effects increase with increasing doses (effect of hypothalamic-pituitary-adrenal axis and bone metabolism)
- Very high doses may mimic effects of OCS

# Dosing ICS's

- Several studies have demonstrated significant variability in response to ICS's
- Some individuals require larger doses for effectiveness
- Rarely they appear not effective (neutrophil predominant inflammation?)

# Comparative Doses of ICS

(Total daily doses in micrograms)

- Beclomethasone

80-160

160-  
320

>320

- Budesonide

180-  
360

360-  
720

>720

- Fluticasone

88-176

176-  
352

>352

80-160	160- 320	>320
180- 360	360- 720	>720
88-176	176- 352	>352

# Other Treatments

- Avoidance of triggers
- Lifestyle changes
- Environmental changes
- Allergy management
- These are all important and can reduce the medication needed if adhered to

# What about alternatives?

- Cromolyn, Nedocromil not as effective and difficult to acquire
- Theophylline requires serum monitoring and has an increased side effect profile
- Leukotriene modifiers not as effective but good safety and easy to use

# What about Add-On Therapy?

- For patients without adequate control on low-medium dose of ICS with good compliance assured and good technique:
- < 5 years: LTRA (monteleukast)
- > 5 years: LABA more effective but LTRA or theophylline acceptable
- For severe asthma not controlled > 12 years: consider omalizumab

# So What's all this Fuss about LABA's?

- The FDA on 2-18-10 issued a Safety Announcement on LABA's that reinforces the prior boxed warning on their use based on further analysis of old data and the Salmeterol Nationwide Surveillance study.
- New requirements are for a Risk Evaluation and Mitigation Strategy for these products.

# Treatment of Exacerbations

- Regular use of ICS prevent and modify exacerbations!
- Intermittent use of ICS at the start of an exacerbation may help in mild asthmatics with big enough dose.
- Increasing the dose of ICS at the start of an exacerbation may help if quadruple the dose (doubling rarely works)
- Test it on each patient before using this strategy

# What about Severe Intermittent Wheezing in the Preschool Child?

- Data on the use of ICS and OCSs is controversial and conflicting in first time wheezers (bronchiolitis?)
- Recurrent severe wheezing with a low asthma predictive index (API) does not seem to be preventable by regular use of ICS or LTRA
- Use in children with high API may be effective in preventing as with older asthma patient

# Is my child going to be short if he takes ICS's?

- No. But he may be short if his asthma isn't controlled.
- Long term studies have shown decrease growth velocity in the first year of ICS use that does not persist with continued use.
- Even with 1 cm decrease in growth in the first year, ultimate adult height is no less than expected for that child

# Safety of ICS

- No concerns at low-medium doses
- Cumulative dose over lifetime may relate to decrease bone density and cataract formation
- Altered hypothalamic-pituitary-adrenal axis is dose related and measurable abnormalities exist at high doses but very few cases of adrenal crisis have been reported (confounding is the use of OCS also)

# Summary

- ICSs reduce impairment domain measures: symptoms (day and night), asthma-control days, rescue-free days, rescue medication use, etc
- ICSs reduce risk domain measures: improved lung function, fewer courses of OCSs, decreased exacerbations, decreased ED and urgent care visits.

# Summary 2

- ICSs were well tolerated in all studies
- Risk of adverse reactions is low (and dose related)
- Small reductions in growth rates were seen but did not persist