Attacking Asthma – Update of Current Therapeutics

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Game Plan

- Brief review of asthma pathophysiology
- Review of standard asthma therapy
- Controversial therapy
  - Long acting beta agonists (LABA)
- Newer therapies
  - (R) - albuterol
  - Leukotriene receptor antagonists
  - Monoclonal anti-IgE antibody
- Update of 2007 NAEPP Asthma Guidelines
Asthma Pathophysiology: Inflammation

- Primarily a chronic inflammatory disease of the airways
  - Primary site of inflammation is endobronchial mucosal lining
  - Inflammation is provoked by foreign molecules entering airway and initiating immune cascade involving multiple receptors / cytokines / chemokines / IgE / NO, etc…
  - Involves mast cells, eosinophils, neutrophils, macrophages, and T lymphocytes
  - Inflammatory cascade can be initiated by both allergic and non-allergic stimulation (cold, pollution, smoking)
Pathophysiology - Inflammatory Cascade

Holtgate ST, Polosa R. The inflammatory response in severe asthma in adults.
Lancet. 2006;368:780-793
Asthma Pathophysiology: Airway Inflammation, cont.

1. Mucosal edema and airway inflammation

2. Submucosal gland hypertrophy with secretions

3. Smooth muscle hypertrophy and contraction
Steroids and Asthma
Corticosteroids in Asthma – Historical Perspective

- Systemic steroids in asthma first reported *NEJM* in 1952
  - Detailed care of 5 pts with refractory asthma
  - Follow-up trial in 1956 demonstrated efficacy in acute asthma, and subsequent trials demonstrated efficacy in chronic asthma
  - Side effects became concerning and eventually limited further use

- Inhaled corticosteroids (beclomethasone and betamethasone) were introduced in early 1970s
  - 2 trials demonstrated efficacy, both published in *BMJ*
Inhaled Corticosteroids - Benefits

- Recommended as first-line therapy in all patients with persistent asthma
- Reduce airway inflammation and hyper responsiveness
- Well demonstrated to:
  - Reduce frequency of days with asthma symptoms
  - Improve lung function
  - Reduce frequency of hospitalization for asthma
  - Reduce risk of life-threatening asthma attacks
In 2000, Canadian group demonstrated that regular use of low-dose inhaled corticosteroids decreased risk of death from asthma

- Case control study with > 30,000 subjects
- Also showed that discontinuation of ICS associated with increased risk of death

Inhaled Corticosteroids – Adverse Effects

- Generally considered to be very safe when used properly and in low / medium doses
- Side effects may occur with systemic absorption and higher doses
  - Systemic absorption associated with poor inhaler technique, lack of spacer, and failure to rinse mouth after use
- Most common side effects are dysphonia (up to 50%) and oral candidiasis
- Less frequent - increased intraocular pressure, cataracts, and osteoporosis
  - All are dose dependent
  - typically only with high doses over prolonged time period
WAP  WAP  WAP

CALVIN! WHAT ARE YOU DOING TO THE COFFEE TABLE?!?

*  

IS THIS SOME SORT OF TRICK QUESTION, OR WHAT?
Inhaled Corticosteroids – Not a Trick Question!

- Inhaled corticosteroids are:
  - highly effective in reducing symptoms, hospitalizations, and preventing death in asthmatic patients
  - safe and easy to use
  - associated with relatively few side effects, particularly at low and medium strengths
  - recommended by the NIH/NHLBI for ALL patients with mild, moderate, and severe persistent asthma.
Long Acting Beta Agonists (LABA) – Background

- Salmeterol and formoterol introduced in U.S. early 1990’s
- Bronchodilator effects persist for more than 12 hours
- Demonstrated superior to short acting BA and placebo in decreasing daytime and nighttime symptoms, decreasing use of rescue inhalers, and improving pulmonary function
- Combination of LABA and ICS shown, for all outcomes, to be superior to doubling dose of the ICS alone
- Recommended in 1997 NIH/NHLBI guidelines for moderate and severe persistent asthma
Long Acting Beta Agonists - Problems

- Shortly after introduction, concern for safety of both short- and long-acting BA arose
  - rising overall asthma mortality - questioned if increasing BA use was causal or secondary to poor asthma control
- Two uncontrolled trials suggested a possible increase in mortality with LABA use
  - SNS study 1991 – United Kingdom
  - SMART trial 1996 – United States
- Meta-analysis of 19 trials published 2006 concluded LABA increase exacerbations and asthma-related deaths
- July 2005 FDA issued public health advisory warning regarding safety concerns of LABA
Salmeterol Nationwide Surveillance Study (SNS)

Conducted in UK 1990-1991 to compare safety of albuterol to LABA salmeterol:

- 25,180 patients
- Asthma severity – 1/6 mild, 2/3 moderate, 1/6 severe

Randomized 2:1 salmeterol bid vs. albuterol qid for 16 weeks

Continued on previous asthma therapy – 69% on ICS, 5% on oral steroids in each group

Salmeterol deaths 12/16,787 (0.07%)
Albuterol deaths 2/8393 (0.02%)
P=0.105
Relative risk = 3.0
1 excess pt death for every 650 pt-years of salmeterol use

Castle W et al. BMJ, 1993;306:1034-1037
SNS trial – Author Conclusions

- Overall incidence of asthma deaths during 16 week trial was not above expected
- Overall asthma control not worsened, and may have improved, in LABA group
- Serious adverse events occurred in those pts in higher risk groups at study entry and were probably due to the disease rather than the treatment
- Further comments regarding LABA and asthma deaths could not be made due to small number of events (14 deaths)
- Recommended ICS for those patients using beta agonists frequently
Salmeterol Multicenter Asthma Research Trial (SMART)

Conducted in 1996 by Glaxo at request of FDA given rising concerns over safety of LABA

- Enrollment target - 60,000 patients
- 6,163 sites in U.S., 1,316 investigators
- Interim analysis planned after 50% enrollment achieved
- Excluded subjects with previous LABA use

Randomized to salmeterol bid vs. placebo for 28 weeks
- Continued all other asthma therapy
- ICS use during study not monitored

Seen initially in investigators clinic, issued 7 month supply of medication, telephone follow-up every 4 weeks

Primary Endpoint: occurrence of respiratory related deaths/respiratory failure
Secondary Endpoints: all cause deaths, asthma deaths/respiratory failure, asthma deaths, respiratory related deaths, all cause deaths/respiratory failure, asthma hospitalizations

SMART Problems—Recruitment and Termination

**Recruitment**

Phase 1 (1996-1999) - via large-scale print/TV/radio advertising

Phase 2 (2000-2003): phase 1 recruitment waned, additional investigators added, and subjects recruited directly by investigators

**Termination**

At interim analysis, though pre-defined criteria for terminating study not met, study sponsor (GlaxoSmithKline) elected to terminate the study after 26,355 subjects enrolled due to preliminary findings in African Americans
SMART – Study Population

- All baseline characteristics similar between groups in LABA and placebo arms
- 72% Caucasian, 18% African American (AA)
- African Americans had significantly greater disease severity at baseline
  - Peak flow 7.2% lower in AA
  - More ER visits and hospitalizations in AA group
- Overall 47% of population on ICS at enrollment
  - 49% of Caucasians on ICS at baseline compared with 38% of AA
  - No monitoring of ICS use during the study period
  - SMART not designed to evaluate effects of ICS on study outcomes
SMART - Results

- Primary endpoint (combined respiratory related deaths/resp failure) - **no difference** between LABA (54 deaths) and placebo (36 deaths) groups
- Small but significant increase in LABA group for 3 secondary endpoints
  - No significant differences between LABA and placebo groups for other secondary endpoints
- Marked difference existed in deaths between recruitment phase 1 (advertising) and phase 2 (direct enrollment):
  - 58.2% of all subjects were recruited in phase 1, and they experienced 81.2% of the adverse outcomes
  - Phase 1 subjects were 3 times more likely to die or have resp failure
  - No difference in percent AA patients in phases 1 and 2
SMART Results, cont

Occurrence of asthma-related deaths by phase and study year

SMART Subgroup Analysis - Race

- Caucasians - no significant differences between LABA and placebo groups for primary or any secondary endpoints

- African Americans - there was a small but significant increase in deaths in the LABA (20 deaths) vs. placebo group (5 deaths) for the primary endpoint
  - 2 secondary endpoints also with increased events in LABA group

**CAUTION**

Post-hoc subgroup analysis involving ~4700 subjects in study initially designed to enroll 60,000 subjects!

Donohue JF. Journal of Family Practice - Supplement, April 2006
SMART Subgroup Analysis – ICS Use

- SMART was not designed to evaluate the effects of ICS on study outcomes
- <50% of subjects were on ICS at time of enrollment, and ICS use was not monitored during the study
- In pts using ICS at enrollment – no differences in number of deaths between LABA and placebo groups for primary or secondary outcomes
- In patients not on ICS at enrollment – significantly increased number of deaths found in 2 secondary endpoints in LABA group
- For ethnic subgroups numbers of deaths too small to draw conclusions regarding ICS use
SMART - Author Conclusions

- No significant differences between treatments for the primary endpoint in the total population
- Small but statistically significant increases in deaths in LABA for 3 secondary endpoints:

“The imbalance occurred largely in the African American subpopulation. Whether this risk in African Americans is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient-level behaviors leading to poor outcomes remains unknown”

SMART – FDA Actions

- November 2005 – FDA requested manufacturers of LABA-containing products to “update their existing product labels with new warnings ... to alert health care professionals and patients that these medicines may increase the chance of severe asthma episodes and death when those episodes occur”

- March 2006 – FDA approved new safety labeling for several salmeterol-containing products
  - No change in labeling for fomoterol

- The labeling for one product, fluticasone/salmeterol, contains a “black-box” warning

- The package insert warnings note that risk of LABA may be increased in African American patients
LABAs – 2007 NHLBI EPR 3

- The Expert Panel recommends that the established, beneficial effects of LABAs for the great majority of patients who have asthma not sufficiently controlled with ICS therapy alone be weighed carefully against the increased risk for potentially deleterious, although uncommon, side effects associated with the daily use of LABAs.

- Therefore, the Expert Panel has modified its previous recommendation (EPR—Update 2002) and has now concluded that, for patients who have asthma not sufficiently controlled with a low-dose ICS alone, the step-up option to increase the ICS dose should be given equal weight to that of the addition of a LABA to ICS.
LABA - Summary

- LABA are not associated with overall worsening of asthma control, and have been shown to reduce asthma symptoms and improve lung function.

- There is a small but significant increase in respiratory-related deaths and asthma related deaths associated with salmeterol.
  - Unclear if also applies to fomoterol - ? Class effect.

- Based on post-hoc analyses in small pt subgroup, the risk of death may be increased in African Americans.

- Concurrent ICS use may be “protective”, although this has not been adequately evaluated in prospective trials.
LABA Recommendations

- LABA are not indicated as first-line treatment of asthma
- **Anti-inflammatory therapy** is the cornerstone of asthma treatment - ensure that airway inflammation is adequately controlled!
- LABA should only be used for patients with moderate or severe persistent asthma that is not controlled on anti-inflammatory agents, in accordance with NHLBI “Stepwise Approach to Asthma”
- Do not use LABA to treat worsening wheezing
  - Likely indicates uncontrolled airway inflammation and need for increased anti-inflammatory therapy
- These recommendations apply to LABA use in asthma only. There are no similar safety concerns for LABA use in COPD at this time
Newer Asthma Therapies

“Try this—I just bought a hundred shares.”
Levalbuterol – Chiral Chemistry

- Chiral Chemical – one that can exist in 2 forms, or \textit{enantiomers}, which are non-super imposable mirror images of each other
  - Example is pair of hands

- Enantiomers often have different chemical activity, as they bind to receptors with different affinities
  - Similar to putting L hand into R glove

- Enantiomers designated (R) or (S) if atoms are oriented in R - or L - hand direction, respectively

- A compound containing equal proportions of each enantiomer is a \textit{racemic} mixture
Racemic Medications

- Many medications exist as racemic mixtures.
  - Usually only the (R) or (S) enantiomer is chemically active
- The inactive enantiomer can be inert, or in some cases toxic
  - thalidomide – (R) form is therapeutic, (S) is teratogenic. Unfortunately the forms are rapidly interconverted within the blood
  - Omeprazole – (S) form is therapeutic, (R) inert. (S) form successfully marketed in 2001 as patent-extension strategy, and was 5th largest-selling medication in U.S. in 2005, with > $6 billion in sales
- As of 1992, FDA requires isolation and separate analysis of all enantiomers of new medications
Levalbuterol

- **Racemic Albuterol = 1:1 mixture of (R) and (S) enantiomers**
  - (R) is active and (S) has **no activity** at B₂ receptor
  - Endogenous epinephrine produced by adrenal medulla also has (R) configuration
- **(R) albuterol is now marketed as levalbuterol**
- **Note that all LABAs are also racemic mixtures of (R) and (S) forms**

**Controversy**

- Is the (S) enantiomer inert, or might it have detrimental effects and toxicities?
- Does the (S) enantiomer interfere with the clinical activity of (R) form?
- Are there meaningful clinical differences between racemic and (R) albuterol?
(S) Albuterol – Problems?

- Some bench top and *in vitro* studies have suggested that (S) albuterol *may* increase smooth muscle contraction, increase airway inflammation, and counteract anti-inflammatory effects of steroids.

- The data, however, are inconsistent, confusing and difficult to interpret, and do no necessarily translate to *in vivo* studies.

- To date no clear or convincing *clinical* evidence that (S) albuterol is detrimental, toxic, or that (S) albuterol interferes with the action of (R) albuterol.
Levalbuterol – Clinical Evidence

- Data from clinical trials are conflicting
- Levalbuterol has been demonstrated to have equal efficacy to racemic albuterol when equal doses of (R) albuterol delivered (i.e. dose of racemic:levalbuerol = 2:1).
- Some studies report significant improvement in spirometry, admission rates and side effects with levalbuterol vs. racemic albuterol
  - Virtually all of these studies sponsored by the manufacturer of levalbuterol
- Other studies find no significant differences in the same parameters/outcomes
- Early studies suggested reduced tachycardia with levalbuterol
- Further studies using equimolar doses clearly show no reduction in tachycardia with levalbuterol
- Clear conclusions difficult to make – further objective studies are needed
Levalbuterol – Cost Issues

- Levalbuterol generally costs 6 times as much as racemic albuterol for equivalent dosing
- Proponents of levalbuterol cite studies that show lower admit rates as justification for higher cost
- Opponents cite studies that show no impact on admit rates with levalbuterol
- Further studies are needed
“...in patients with asthma, no consistent differences have been found with (R) albuterol (i.e. levalbuterol) compared to with (R,S) albuterol in bronchodilation, bronchoprotection, or side effects, whereas (S) albuterol is inactive with no documented adverse effects...in view of it’s clinical equivalence and considerably higher cost compared with the normal (R,S) albuterol, this treatment cannot be recommended in any patient groups.” 

-Peter J Barnes, DM, DSc, Imperial College, London, UK

Am J Respir Crit Care Med 2006;174:965-974
Leukotriene Receptor Antagonists (LTRAs)

- Leukotrienes are active in the pathogenesis of asthma
  - formed via the metabolism of arachidonic acid along the 5-lipoxygenase pathway

- LTRAs
  - block the formation of leukotrienes
  - were the first class of asthma agents developed after ICS
  - were the first asthma therapy to target a specific mediator

- 3 LTRAs are available in the US
All 3 LTRAs have been studied as primary asthma controller medications and, compared to placebo:
- improve lung function
- decrease asthma symptoms
- reduce need for rescue inhalers
- reduce frequency of exacerbations

www.uptodate.com
LTRAs - Compared to ICS

- LTRAs exert anti-inflammatory effects, though not as effectively as ICS
- In clinical trials, ICS have typically proven superior, though LTRAs are effective and some studies show no differences
- LTRAs are considered alternative first-line anti-inflammatory/controller medications for patients who can’t or won’t take ICS
LTRAs – Compared to LABA

- LTRAs have been compared to LABA when added to ICS for inadequately controlled asthma.
- Most studies show that LABAs are superior in improving asthma control and reducing asthma exacerbations in this setting.
- Possible adverse effects of LABAs must be taken into consideration in deciding appropriate agent to use.
LTRAs - Recommendations

- LTRAs can be used as monotherapy in mild or moderate-persistent asthma in patients who can’t or won’t use ICS
  - ICS remain the first-choice
- LTRAs are efficacious when added to ICS for inadequately controlled moderate- or severe-persistent asthma
  - LABAs are more effective in this role
- LTRAs should be used for 1-2 months before making conclusion regarding effectiveness
Omalizumab

- Recombinant humanized IgG monoclonal anti-IgE Ab that binds to IgE, forming inert IgE:anti-IgE complexes.
- Reduces free serum IgE by 89-99%
- Inability of free IgE to bind to mast cells limits release of allergic response mediators (cytokines, leukotrienes, histamines, etc...), preventing immediate and delayed asthmatic response

Omalizumab – Clinical Trials

- 4 randomized trials demonstrated efficacy compared to placebo:
  - Fewer asthma exacerbations per pt
  - Lower percentage of patients had asthma exacerbations
  - Lower dose of ICS needed to control symptoms
  - Improved quality of life

- Approved by FDA 2003 for
  - > 12 yo
  - moderate- or severe-persistent allergic asthma (+ skin test or RAST)
  - inadequate control by ICS
  - total serum IgE 30-700 IU/ml

- Administered as subcutaneous injection q2-4 weeks
Omazilumab - Concerns

**Cost**
- depends on dose, which depends on total serum IgE and body wt
- range from $4,000 - $20,000/yr, with avg $12,000/yr

**Safety Concerns**
- In clinical trials, cancer developed in more patients in omazilumab group than placebo group (0.5% vs. 0.2%)
- Anaphylaxis - initially reported in 0.1% in clinical trials, but post-marketing experience with anaphylaxis occurring up to 24 hrs after a dose, and occurring after any dose, even if there was no reaction to the first dose.
- 2/2007 - FDA recommends boxed label warning regarding anaphylaxis risk
Omazilumab – Role in Asthma Therapy

- No recommendation made in 2003 NHLBI guidelines regarding use
  - “...the development of humanized monoclonal antibodies has become a possible treatment”

- Consider use in patient with moderate- or severe-persistent allergic asthma with ongoing symptoms despite treatment with adequate doses of ICS and LABAs.
NAEPP/NHLBI Guidelines

- 3rd full report released late 2007
- http://www.nhlbi.nih.gov/guidelines/asthma
Highlights of Past NAEPP Guidelines

- 1991 – objective measurement of lung function, environmental control, pharmacologic therapies, patient education
  - included “stepwise” approach to therapy with increasing therapy for worsening disease
- 1997 – paradigm of “controllers” and “quick relievers”, new medications including long-acting beta agonists (LABAs) and leukotriene modifiers
- 2002 (update) – stressed concept of asthma as inflammatory disease, inhaled corticosteroids (ICS) as mainstay of control for persistent asthma
## Asthma Classification – NHLBI 2002

### Classification of Asthma Severity: Clinical Features Before Treatment

<table>
<thead>
<tr>
<th>Classification of Asthma Severity: Clinical Features Before Treatment</th>
<th>Days With Symptoms</th>
<th>Nights With Symptoms</th>
<th>PEF or FEV₁*</th>
<th>PEF Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 4</strong></td>
<td>Severe Persistent</td>
<td>Continual</td>
<td>Frequent</td>
<td>≤60%</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>Moderate Persistent</td>
<td>Daily</td>
<td>≥5/month</td>
<td>&gt;60%-&lt;80%</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>Mild Persistent</td>
<td>3-6/week</td>
<td>3-4/month</td>
<td>≥80%</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td>Mild Intermittent</td>
<td>≤2/week</td>
<td>≤2/month</td>
<td>≥80%</td>
</tr>
</tbody>
</table>

* Percent predicted values for forced expiratory volume in 1 second (FEV₁) and percent of personal best for peak expiratory flow (PEF) (relevant for children 6 years old or older who can use these devices).
Stepwise Approach to Asthma Management

**Step 1**
**Mild Intermittent**
- < 2 days/week
- < 2 nights/month
- No daily meds

**Step 2**
**Mild Persistent**
- > 2/week, < 1/day
- > 2 nights/month
- Low dose Inhaled Corticosteroid

**Step 3**
**Moderate Persistent**
- Daily symptoms
- > 1 night/week
- Medium dose Inhaled Corticosteroid + Long Acting Beta Agonist if needed

**Step 4**
**Severe Persistent**
- Continual symptoms
- High dose Inhaled Corticosteroid + Long Acting Beta Agonist + Systemic steroid if needed

NIH/NHLBI Guideline Update. June 2002; NIH publication 02-5075
2007 NAEPP Guidelines – What’s New?

- Main focus changes to assessment of severity and control
  - Severity - intrinsic intensity of the disease process
    - assessed at initiation of treatment
    - dynamic – may change over time
    - accurate assessment guides selection of initial therapy
  - Control - reflects how well current therapies are working
    - assessed for patients already on asthma therapy
    - accurate assessment guides changes in therapy
  Severity and control are treated separately in the 2007 guidelines
  - Note new guidelines use 3 age categories (0-4, 5-11, >12) rather than 2 (<5, ≥ 5) used previously
Impairment and Risk

- For both severity (not on therapy) and control (already on therapy), impairment and risk are assessed to classify disease process and select therapy.

  - Impairment – frequency and intensity of symptoms the pt is currently experiencing
    - symptoms (day and night), use of beta agonists for symptom relief, restrictions on normal activity, and current lung function
    - very similar to the assessment in previous guidelines
  
  - Risk – likelihood of exacerbations, risk of reduction in lung function, risk of adverse medication effects
    - new emphasis in 2007 guidelines
# Severity and Control

<table>
<thead>
<tr>
<th>Severity</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic intensity of disease process</td>
<td>Degree to which:</td>
</tr>
<tr>
<td>Assessed to initiate therapy</td>
<td>- Signs an symptoms are minimized due to therapy</td>
</tr>
<tr>
<td></td>
<td>- Goals of therapy are met</td>
</tr>
<tr>
<td></td>
<td>Assessed to monitor and adjust therapy</td>
</tr>
<tr>
<td>Include both Current Impairment and Future Risk</td>
<td>Includes both Current Impairment and Future Risk</td>
</tr>
<tr>
<td>Components of Severity</td>
<td>Classification of Asthma Severity ≥12 years of age</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td>Persistent</td>
</tr>
<tr>
<td>8–19 y 85%</td>
<td>Mild</td>
</tr>
<tr>
<td>20–39 y 80%</td>
<td>Moderate</td>
</tr>
<tr>
<td>40–59 y 75%</td>
<td>Severe</td>
</tr>
<tr>
<td>60–80 y 70%</td>
<td></td>
</tr>
<tr>
<td><strong>Intermittent</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>&lt;2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>&gt;2 days/week but not nightly</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptom control (not prevention of EIB)</td>
<td>Daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>• Normal FEV₁ between exacerbations</td>
<td>Daily</td>
</tr>
<tr>
<td>• FEV₁ &gt;80% predicted</td>
<td>Several times per day</td>
</tr>
<tr>
<td>• FEV₁/FVC normal</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>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 FEV₁.</td>
</tr>
<tr>
<td>Recommended Step for Initiating Treatment (See “Stepwise Approach for Managing Asthma” for treatment steps.)</td>
<td>Step 1 Step 2 Step 3 Step 4 or 5 and consider short course of oral systemic corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1/year (see note)</td>
<td>≥2/year (see note)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td></td>
</tr>
</tbody>
</table>

In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.
<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (≥12 years of age)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
<td>Not Well Controlled</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>1–3x/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some limitation</td>
</tr>
<tr>
<td>Short-acting β2-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
<td>60–80% predicted/ personal best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td>ATAQ ≤0.75* 0 ≥20</td>
<td>1–2 ≥1.5 16–19</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year</td>
<td>≥2/year (see notes)</td>
</tr>
<tr>
<td>Risk</td>
<td>Evaluation requires long-term follow-up care.</td>
<td></td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommended Action for Treatment</strong></td>
<td><strong>Maintain current step.</strong></td>
<td><strong>Step up 1 step.</strong></td>
</tr>
<tr>
<td>(See “Stepwise Approach for Managing Asthma” for treatment steps.)</td>
<td><strong>Regular follow-up at every 1–6 months to maintain control.</strong></td>
<td><strong>Re-evaluate in 2–6 weeks.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Consider step down if well controlled for at least 3 months.</strong></td>
<td><strong>For side effects, consider alternative treatment options.</strong></td>
</tr>
</tbody>
</table>
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 2
Preferred: Low-dose ICS + LABA OR Medium-dose ICS
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: High-dose ICS + LABA
AND Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND Consider Omalizumab for patients who have allergies

Step 6
Step up if needed (first, check adherence, environmental control, and comorbid conditions)

Assess control
Step down if possible (and asthma is well controlled at least 3 months)

Each Step: Patient education, environmental control, and management of comorbidities. Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
2007 Guidelines – Case Example

- 18 yo male with newly diagnosed asthma presents for his first visit. He is not on any medications

- Assess severity
  - Impairment – + daily symptoms, night awakenings 1-2 X/month, no SABA use, minor interference with normal activities, Lung fxn FEV1 85%, FEV1/VC normal
  - Risk – 1 exacerbation in past year requiring steroids
18 yo Male - Classification

The patient’s asthma severity is based on the most severe category. Therefore this patient is categorized with moderate persistent asthma. Pt would be started on medications in Step 3.

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3-4x/month</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily, and not more than 1x on any day</td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–19 y 85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39 y 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59 y 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69 y 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁/FVC normal</td>
</tr>
<tr>
<td>FEV₁/FVC normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year (see note)</td>
<td>≥2/year (see note)</td>
</tr>
<tr>
<td>Relative annual risk of exacerbations may be related to FEV₁.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommended Step for Initiating Treatment (See “Stepwise Approach for Managing Asthma” for treatment steps.)

Step 1

Step 2

Step 3

Step 4 or 5

In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.
### 18 yo Male – Initial Therapy

#### Intermittent Asthma
- Consult with asthma specialist if step 4 care or higher is required.
- Consider consultation at step 3.

#### Step 1
- **Preferred:** SABA PRN
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

#### Step 2
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, Theophylline, or Zileuton

#### Step 3
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, Theophylline, or Zileuton

#### Step 4
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, Theophylline, or Zileuton

#### Step 5
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, Theophylline, or Zileuton

#### Step 6
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Low-dose ICS + LABA OR Medium-dose ICS + either LTRA, Theophylline, or Zileuton

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#### Table: Estimated Comparative Daily Dosages for Inhaled Corticosteroids for Youths ≥12 Years of Age and Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult</th>
<th>Medium Daily Dose Adult</th>
<th>High Daily Dose Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide DPI</td>
<td>180–600 mcg/puff</td>
<td>&gt;600–1,200 mcg/puff</td>
<td>&gt;1,200 mcg/puff</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>&gt;88–264 mcg</td>
<td>&gt;284–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>&gt;100–300 mcg</td>
<td>&gt;300–500 mcg</td>
<td>&gt;500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI</td>
<td>200 mcg/puff</td>
<td>200 mcg</td>
<td>400 mcg</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>75 mcg/puff</td>
<td>300–750 mcg</td>
<td>&gt;750–1,500 mcg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;1,500 mcg</td>
</tr>
</tbody>
</table>

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**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of attack, as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of ExB) generally indicates up-treatment.
18 yo Male - 4 week Follow-up

- Assess asthma control
  - Impairment - symptoms 2x/week, nighttime awakenings 2x/week, no interference with normal daily activity, SABA use 2x/week, lung fxn FEV1 85%, ACT score 17
  - Risk - no exacerbations, no treatment-related side effects
# 18 yo Male Follow-Up Changes

## Classification of Asthma Control (>12 years of age)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose Adult</th>
<th>Medium Daily Dose Adult</th>
<th>High Daily Dose Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA</td>
<td>60–240 mcg</td>
<td>&gt;240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA</td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI:</td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
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<td>44, 110, or 220 mcg/puff</td>
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<td>200 mcg</td>
<td>400 mcg</td>
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<tr>
<td>Mometasone DPI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>300–750 mcg</td>
<td>&gt;750–1,500 mcg</td>
<td>&gt;1,500 mcg</td>
</tr>
</tbody>
</table>

## Stepwise Approach for Managing Asthma

**Step 5**
- **Preferred:** High-dose ICS + LABA + oral corticosteroid AND Consider Omalizumab for patients who have allergies
- **Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 6**
- **Preferred:** Consider Omalizumab for patients who have allergies

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**Recommended Action for Treatment**

(See “Stepwise Approach for Managing Asthma” for treatment steps.)

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
- For side effects, consider alternative treatment options.
Conclusions

- Asthma is an inflammatory disease
- Cornerstone of asthma therapy are inhaled corticosteroids for mild/mod/severe persistent disease
  - Leukotriene antagonists may be used if ICS are not tolerated
- LABA can be added in mod/severe persistent asthma that is not adequately controlled on ICS alone
  - Safety concerns: poor studies suggest possibility of increased deaths in African-American subgroup
  - Effects of ICS + LABA not studied prospectively
Conclusions, cont

Levalbuterol and racemic albuterol have equal efficacy.
- To date no studies have convincingly demonstrated any advantage of levalbuterol
- Levalbuterol has not been shown to produce less tachycardia than racemic albuterol
- Levalbuterol is considerably more expensive

Omazilumab can be considered in mod/severe persistent allergic asthma not adequately controlled with ICS/LABA/LTRA
- Very expensive
Welcome to Marlboro Country.

Till death do we part.

“Well, it’s a good thing you changed cigarettes, Frank. You only have cancer light.”