

Asthma Pharmacotherapy: Stepwise Approach to Managing Asthma



Webinar for
Michigan Center for Clinical Systems Improvement
(Mi-CCSI)

Karen Meyerson, MSN, APRN, NP-C, AE-C

Director, Commercial Care Management

Priority Health

September 30, 2016

Asthma Pharmacotherapy

Quick-relief

- Short-acting beta-agonists
- Inhaled anticholinergics
- Systemic corticosteroids

Long-term control

- Corticosteroids
- Cromolyn sodium
 - Mast cell stabilizer
 - Only available in nebulized form
- Long-acting inhaled beta-agonists
- Theophylline
- Leukotriene Receptor Antagonists (LTRA)

Quick-Relief Medications

- Short-acting beta₂-agonists (SABA): albuterol (Pro-Air®, Ventolin®, Proventil®); levalbuterol (Xopenex®)
- Relax bronchial smooth muscles
- Short-acting
 - ◆ Work within 10 - 15 minutes
 - ◆ Last 4 - 6 hours
- Bind to and activate beta₂ receptors in cardiac and smooth muscle tissues
 - ◆ Cause bronchodilation in lungs
 - ◆ Side effects can include shakiness (tremors), tachycardia
- (Older) beta-blockers are contraindicated in asthma as they can cause the opposite effect - bronchoconstriction
- Danger of over-use

Short-acting β_2 -agonists (SABA)

- Most effective medication for relief of acute symptoms



RED FLAG

- more than 2 canisters per year
- Regularly scheduled use not generally recommended
 - ◆ May “lower” effectiveness
 - ◆ May increase airway hyperresponsiveness

Anticholinergics

- Ipratropium bromide (Atrovent) or ipratropium bromide & albuterol (Combivent)
- Not specifically indicated for “usual” quick-relief medication in asthma
 - ◆ contrast with COPD
- Now well-studied as adjunct to beta-agonists in emergency departments
 - ◆ i.e., acute exacerbations

Long-term Control Medications

- Inhaled corticosteroids (ICS): fluticasone propionate (Flovent®); beclomethasone (QVAR®); budesonide (Pulmicort®); mometasone (Asmanex®); ciclesonide (Alvesco®); triamcinolone (Aerospan®), fluticasone furoate (Arnuity®)
- Combination products (inhaled corticosteroids and long-acting beta₂-agonists or ICS/LABA):
 - ◆ fluticasone & serevent (Advair®)
 - ◆ budesonide & formoterol (Symbicort®)
 - ◆ mometasone & formoterol (Dulera®)
 - ◆ fluticasone furoate & vilanterol (Breo®)
- Leukotriene receptor antagonist (LTRA): montelukast (Singulair®), zafirlukast (Accolate®), zileuton (Zyflo®)
- Methylxanthines: theophylline (Theo-Dur®, Slo-bid®)
- Anti-IgE blocker: omalizumab (Xolair®)

Long-term Control Medications

- Should be taken daily and chronically to maintain control of persistent asthma and to prevent exacerbations:
 - ◆ Soothes airway swelling
 - ◆ Helps prevent asthma flares - very effective for long-term control but must be taken daily
 - ◆ Often under-used

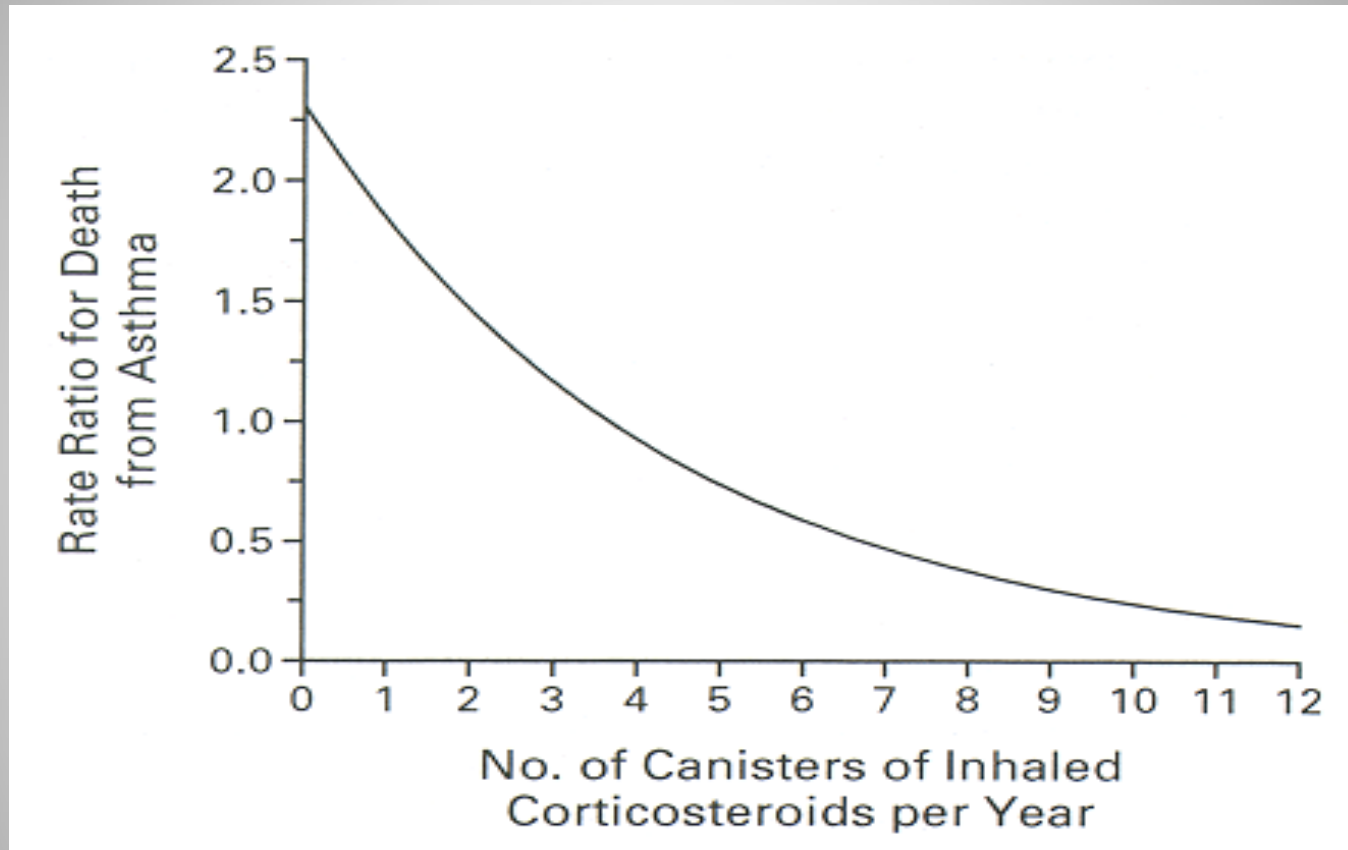
Inhaled Corticosteroids (ICS)

- Actions:
 - ◆ potentiate β -receptor responsiveness
 - ◆ reduce mucus production and hypersecretion
 - ◆ inhibit inflammatory response at all levels
- Best effects if started early after diagnosis
- Symptomatic and spirometric improvement within 2 weeks
 - ◆ maximum effects within 4-8 weeks

Inhaled Corticosteroids (ICS) (continued)

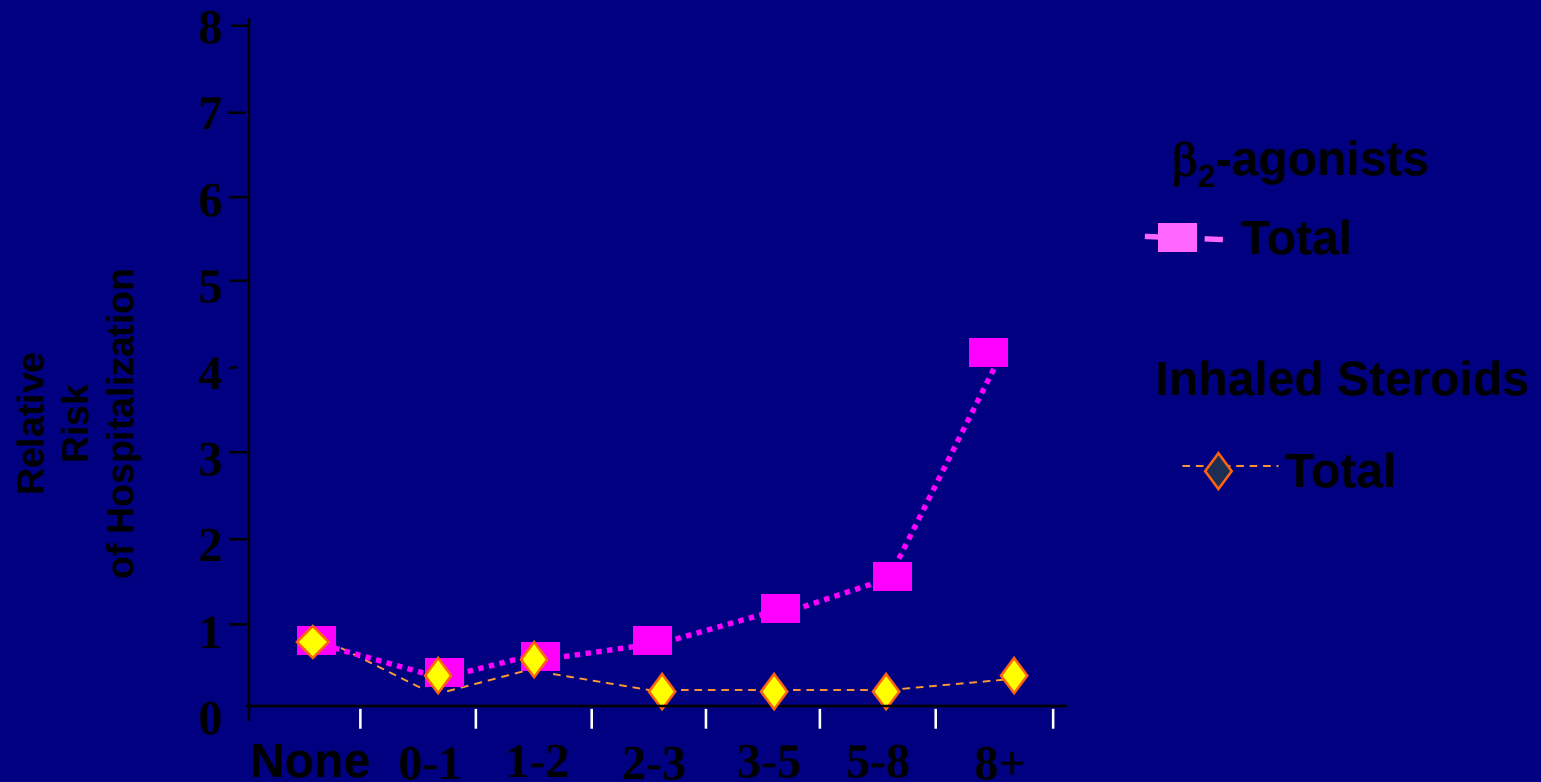
- THE most effective long-term control medication for persistent asthma
- Small risk for adverse events at usual doses
 - ◆ Risk can be reduced even further by:
 - Using spacer and rinsing mouth
 - Using lowest effective dose
 - Using with long-acting β_2 -agonist when appropriate
 - Monitoring growth in children

Low dose ICS and the Prevention of Asthma Deaths



- ICS protects patients from asthma-related deaths
- Users of > 6 canisters/yr. had a death rate ~ 50% lower than non-users of ICS
- Death rate decreased by 21% for each additional ICS canister used during the previous year.

ICS May Help Prevent the Risk of Asthma Related Hospitalizations



Short-acting β_2 prescriptions dispensed per person-year

Inhaled Corticosteroids (ICS) (continued)

- Hypothalamic-pituitary-adrenal (HPA) suppression
 - ◆ Not seen in usual doses
- Cataracts
 - ◆ Not seen in usual doses
- Long bone growth
 - ◆ Growing understanding of this risk
 - ◆ Childhood Asthma Management Program (CAMP) study (2000)* showed small, transient reduction in growth velocity from ICS
 - ◆ Update (2012)** showed growth reduction persisted as lowered adult height (1.2 cm) – need to weigh risks & benefits
- Osteoporosis/Bone Fractures
 - ◆ Some attention at high doses, high-risk patients
- Candidiasis (thrush)
- Dysphonia (hoarseness)

*N Engl J Med. 2000 Oct 12;343(15):1054-63

**N Engl J Med 2012 367(10):904-912.

Leukotriene Receptor Antagonists (LTRA)

- Two mechanisms
 - ◆ 5-lipoxygenase inhibitors
 - zileuton (Zyflo®)
 - ◆ Cysteinyl leukotriene receptor antagonists
 - zafirlukast (Accolate®), montelukast (Singulair®)
- Indications
 - ◆ Generally, alternative therapy in mild persistent asthma or as add-on in higher stages
 - Improve lung function
 - Decrease short-acting β_2 -agonist use
 - Prevent exacerbations

Methylxanthines (Theophylline) (continued)

- Places in therapy:
 - ◆ When inhaled corticosteroids not possible
 - ◆ Patients who can't/won't use inhalers
 - ◆ Additive therapy at later stages
- Adverse Drug Reactions/Serum Levels
 - ◆ Therapeutic Range 5-15 mcg/mL, or 10-20 mcg/mL
 - ◆ Levels > 20 mcg/mL: nausea, vomiting, diarrhea, headache, irritability, insomnia, tachycardia
 - ◆ Levels > 30 mcg/mL: seizures, toxic encephalopathy, hyperthermia, brain damage
- Drug Interactions: PLENTY!!

Long-Acting β_2 -Agonists

- Not a substitute for anti-inflammatory therapy
- Not appropriate for monotherapy



RED FLAG

- Literature supporting role in addition to inhaled corticosteroids
- Not for acute symptoms or exacerbations
- Salmeterol (Serevent®) first of class in US (in Advair®)
- Newer LABAs: formoterol (Foradil®) & vilanterol (in Breo®)
 - ◆ Newer long-acting beta-agonists
 - ◆ Have rapid onset and long duration
 - ◆ Formoterol is available in combination with inhaled steroid in Symbicort® & Dulera® (BID dosing), vilanterol is in Breo® (qd dosing)

Long-Acting β_2 -Agonists

- Salmeterol Multicenter Asthma Research Trial (SMART)
- A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.
- Nelson HS, Weiss ST, Bleecker ER, et al.
Chest 2006; 129:15-26.



CHEST

Original Research

ASTHMA

The Salmeterol Multicenter Asthma Research Trial*

A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

Harold S. Nelson, MD; Scott T. Weiss, MD, MS; Eugene R. Bleecker, MD; Steven W. Yancey, MS; and Paul M. Dorinsky, MD; and the SMART Study Group

Long-Acting β_2 -Agonists (LABAs)

- Patients > 12 years old with asthma
- Sought to evaluate the effects of salmeterol or placebo added to usual asthma care on
 - ◆ respiratory and asthma related deaths
 - ◆ life-threatening episodes
- Initial aim to enroll 30,000 patients; later changed with aim to enroll 60,000

Long-Acting β_2 -Agonists (LABAs)

- Increase in adverse events in salmeterol group during SMART trial:
 - ◆ Particularly in those recruited in Phase 1
 - ◆ Particularly among African-Americans who were noted to have markers of more severe asthma and less likely to be using ICS
- Increase in adverse events in salmeterol group:
 - ◆ Due to adverse effect of salmeterol?
 - ◆ Due to inappropriate bronchodilator use? (affected patients were more severe at baseline and less likely to be using ICS)

FDA Safety Requirements for Long-Acting β_2 -Agonists (LABAs) in Asthma

- The use of LABAs is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
- LABAs should be used for the **shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved**. Patients should then be maintained on an asthma controller medication.
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid **should use a combination product** containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.

Long-Acting β_2 -Agonists (LABAs)

- Conclusions:

- ◆ Black Box warning
- ◆ Do not use long-acting bronchodilators alone
- ◆ Always use with inhaled corticosteroids
- ◆ Newer Data:
 - LABAs when used with inhaled corticosteroids are helpful. Multiple reviews/meta-analyses suggest that long-acting beta-agonists + inhaled corticosteroids reduce asthma hospitalizations compared to inhaled corticosteroids alone.
 - Emphasize the weakness of the primary data in terms of statistical strength, simply because asthma-related deaths and intubations are so rare.

Patients Are Candidates for Maintenance Therapy if The “RULES OF TWO”™* Apply...

- They are using a quick-relief inhaler more than **2 times per week**
- They awaken at night due to asthma more than **2 times per month**
- They refill a quick-relief inhaler Rx more than **2 times per year**

*“RULES OF TWO”™ is a trademark of the Baylor Health Care System.

Out of Control!

Rules of Two TM

- If your patient can answer “YES” to ANY of these questions, his/her asthma is probably not under good control.
- These rules define persistent asthma.

Asthma Severity

- *Intermittent*
- *Mild Persistent*
- *Moderate Persistent*
- *Severe Persistent*

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN

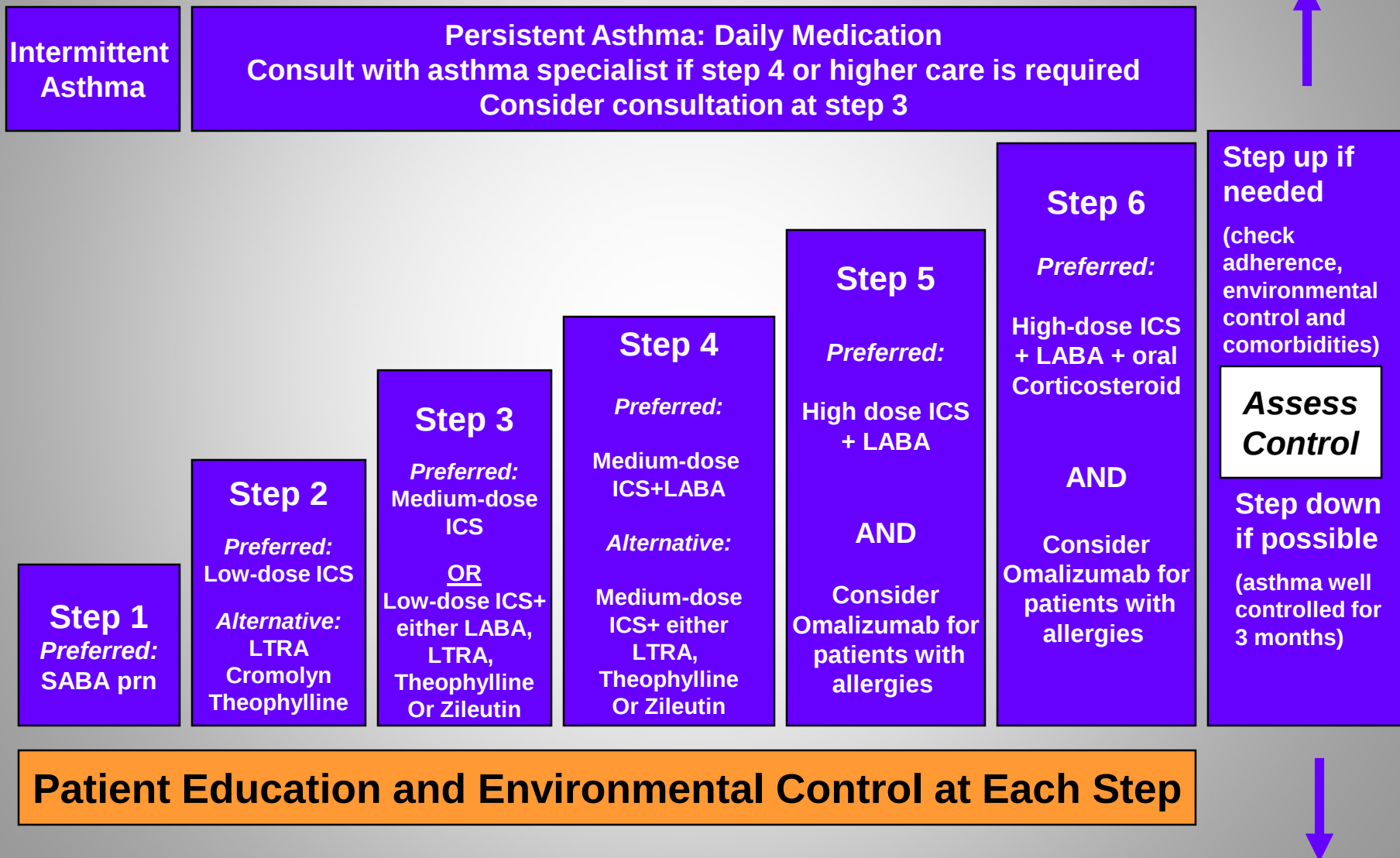
YOUTHS ≥ 12 YEARS AND ADULTS

EPR-3, p74, 344

Components of Severity		Classification of Asthma Severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV ₁ /FVC 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤2 days/week	>2 days/week not daily	Daily	Continuous
	Nighttime Awakenings	≤2x/month	3-4x/month	>1x/week not nightly	Often nightly
	SABA use for sx control	≤2 days/week	>2 days/week not daily	Daily	Several times daily
	Interference with normal activity	none	Minor limitation	Some limitation	Extremely limited
	Lung Function	• Normal FEV ₁ between exacerbations • FEV ₁ > 80% • FEV ₁ /FVC normal	• FEV ₁ >80% • FEV ₁ /FVC normal	• FEV ₁ >60% but< 80% • FEV ₁ /FVC reduced 5%	• FEV ₁ <60% • FEV ₁ /FVC reduced> 5%
Risk	Exacerbations (consider frequency and severity)	0-2/year > 2 /year 			
		Frequency and severity may vary over time for patients in any category Relative annual risk of exacerbations may be related to FEV			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3	Step 4 or 5
		In 2 -6 weeks, evaluate asthma control that is achieved and adjust therapy accordingly Consider short course of oral steroids			

STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS > 12 YEARS AND ADULTS

EPR-3, p333-343



Asthma Control

The purpose of periodic assessment and ongoing monitoring is to determine whether the goals of asthma therapy are being achieved and asthma is controlled.

- *Well Controlled*
- *Not Well Controlled*
- *Very Poorly Controlled*

ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN

YOUTHS $\geq$ 12 YEARS OF AGE AND ADULTS

EPR-3, p77, 345

Components of Control		Classification of Asthma Control		
IMPAIRMENT	Symptoms	Well Controlled	Not Well Controlled	Very Poorly Controlled
		≤ 2 days/week	> 2 days/week	Throughout the day
	Nighttime awakenings	≤ 2 /month	1-3/week	≥ 4 /week
	Interference with normal activity	none	Some limitation	Extremely limited
	SABA use	≤ 2 days/week	> 2 days/week	Several times/day
	FEV ₁ or peak flow	$> 80\%$ predicted/ personal best	60-80% predicted/ personal best	$< 60\%$ predicted/ personal best
RISK	Validated questionnaires ATAQ/ACT	0/ ≥ 20	1-2/16-19	3-4/ ≤ 15
	Exacerbations	0- 1 per year	2 - 3 per year	> 3 per year
	Progressive loss of lung function	Evaluation requires long-term follow up care		
	Rx-related adverse effects	Consider in overall assessment of risk		
Recommended Action For Treatment		•Maintain current step •Consider step down if well controlled at least 3 months	•Step up 1 step •Reevaluate in 2 - 6 weeks	•Consider oral steroids •Step up (1-2 steps) and reevaluate in 2 weeks

Current Therapy

- **Use Asthma Guidelines as a guide**
- **Poor adherence with inhaled therapy**
- **No curative therapy**
- **Many patients remain poorly controlled**
- **Recognition of different phenotypes of asthma**

New/Upcoming Asthma Therapies

- Recognition that there are different phenotypes or endotypes of asthma
 - ◆ Phenotype – observable characteristics or clinical presentation (e.g., transient vs. persistent wheezing)
 - ◆ Endotype – a subtype of a condition defined by a distinct pathophysiological mechanism
- As treatments become more specific, targeting specific inflammatory cells (such as blockade of specific cytokines or kinases) may be effective in the treatment of asthma
- Because new therapies are likely to be very expensive (especially antibodies) it will become increasingly important to recognize responder patients

New Long-Acting Bronchodilators

- Prevention and relief of bronchoconstriction
- LABAs offered 12 hour action
 - ◆ Salmeterol (Serevent®), formoterol (Foradil®)
- Now Ultra-LABAs in development with 24-hour action
 - ◆ indacaterol, carmoterol, vilanterol and olodaterol.

Risks of LABAs

- Increased risk of overall death if monotherapy
- Evidence supports LABA + ICS in a single inhaler device for patient with mod/severe asthma

Thorax 2012; 67: 67 342-349

ProAir RespiClick®

albuterol sulfate dry powder inhaler



- Breath actuated

Side Effects

- Back pain
- Body aches and pains
- Upset stomach
- Heart racing
- Urinary tract infection
- Shakiness

Arnuity Ellipta® fluticasone furoate



- Approved August 2014
- Once daily maintenance therapy of asthma in those 12 and older
- Normal dose is one inhalation daily
- Starting dose is 100mcg
- May increase to 200mcg after 2 weeks

Side Effects

- Upper infections
- Nasopharyngitis
- Headache
- Bronchitis
- Oral candidiasis

LABA/Corticosteroid

- **New products aimed for ease of use and adherence to therapy**
- **One inhalation/once daily**

Breo Ellipta®

fluticasone furoate/vilanterol



- FDA approval 4/30/2015 for ages 18 and older
- LABA warning continues
- Once daily inhalation therapy for individuals with asthma
- Side Effects - Headache, nasopharyngitis, pneumonia, fractures

Respimat®

New Inhalation Device

SMI (Soft Mist Inhaler)



Respimat Medications:

- Combivent®
 - albuterol and ipratropium (quick-relief)
- Spiriva®
 - Tiotropium (LAMA)
- Stiolto®
 - Tiotropium/olodaterol (LAMA/LABA)

Spiriva Respimat® (tiotropium)

- New indication for asthma
- Dose 1.25mcg/actuation = 2 actuations once daily
- Add-on maintenance bronchodilator treatment
- Once-daily maintenance treatment for patients with asthma >12 years
- Not for the relief of acute bronchospasm
- Can be used in patients who remain symptomatic on ICS/LABA
- Adverse reactions: pharyngitis, cough, headache, palpitations, dizziness, dysphonia



Xolair® (omalizumab)

Anti-IgE Therapy

- Biologic antibody therapy binds IgE in the circulation and prevents it from activating mast cells and basophils.
- In moderate to severe asthma, anti-IgE therapy reduced exacerbation rate and reduced steroid dose needed.
- Anti IgE therapy is recommended as an add-on to optimized standard therapy in individuals 12 years and older who need continuous or frequent treatment with oral corticosteroids.
- Elevated serum IgE 30-700 IU/ml
- Positive allergy test



Xolair® Indication

- Omalizumab (Xolair) is indicated for adults and adolescents 12 years of age and above
 - ◆ With moderate to severe, persistent asthma
 - ◆ Who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen
 - ◆ Whose symptoms are inadequately controlled with inhaled corticosteroids
 - ◆ Elevated serum immunoglobulin E (IgE) level (≥ 30 -700 IU/mL)
- Xolair has been shown to decrease the incidence of asthma exacerbations in these patients
- Safety and efficacy have not been established in other allergic conditions

Nucala® (mepolizumab)

- Indicated for the maintenance treatment of asthma in people over 12 years whose asthma is not otherwise controlled on current asthma medicines
- For patients with an eosinophilic phenotype – eosinophils are responsible for airway inflammation in asthma
- Helps prevent exacerbations
- Reduces blood eosinophils in patients with severe eosinophilic asthma (>150 cells/microliters at start or >300 anytime in past 12 months).
- Dose: 100 mg subcutaneously q 4 weeks

Nucala® (mepolizumab)

- Anti-interleukin 5 (IL-5) targeted therapy for individuals with severe asthma with an eosinophilic phenotype
- Patients 12 years and older with severe asthma who have:
 - Current therapy (high dose ICS and additional controller(s))
 - Exacerbation history ≥ 2 in prior 12 months*
 - Blood eosinophil levels ≥ 150 cells/ μ L
 - Obtain CBC with differential
- Once-monthly fixed dose SC injection
- Adverse reactions: anaphylaxis, headache, dizziness, back pain, local reaction at injection site

*Oral steroids, hospitalization(s) or ED visit(s)

Cinqair® (reslizumab)

- Anti-interleukin-5 monoclonal antibody
- Intravenous infusion
- Indicated for maintenance treatment of patients with severe asthma 18 years and older
- Binds to human IL-5 and prevents it from binding to IL-5 receptor, thereby reducing eosinophilic inflammation
- Dose is 3 mg/kg every 4 weeks
- Adverse reactions: anaphylaxis, cancer and muscle pain

Bronchial Thermoplasty

- Indicated for treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and LABAs
- Performed with a bronchoscope – involves the delivery of controlled, therapeutic radiofrequency energy to the airway wall
- This results in heating of the tissue and reduces the amount of smooth muscle present in the airway way
- Requires 3 separate bronchoscopic procedures
- Reduces asthma exacerbations, ER visits and hospitalizations

Timothy Grass Extract

Grastek®

- Used for grass pollen-induced allergic rhinitis confirmed by positive allergy testing
- Dose one tablet sublingual daily
- First dose in allergy office (observed for 30 minutes), then taken once daily at home
- Leave under tongue for at least 1 minute
- Start 12 weeks before grass season
- Ages 5 - 65
- Do not use in severe or uncontrolled asthma



Timothy Grass Extract Grastek®

- Side effects
 - ◆ Throat irritation
 - ◆ Itchy ears
 - ◆ Oral itching
 - ◆ Mouth edema
 - ◆ Headache
- Stop taking if trouble breathing, throat tightness or swelling, trouble swallowing, dizziness, rapid heartrate, severe stomach symptoms
- Possibility of systemic (anaphylactic) reaction (lower risk than immunotherapy injections)
- Offer an EpiPen for home use



Grass Pollen Extract Oralair®

- Used for treatment of grass pollen-induced allergic rhinitis confirmed by positive allergy testing
- 5 grass species included
- Dose: one sublingual tab daily
- Ages 10 - 65
- Do not use in uncontrolled asthma

Grass Pollen Extract Oralair®

- Side Effects
 - ◆ Oral itching
 - ◆ Throat irritation
 - ◆ Ear itching
 - ◆ Edema mouth
- Stop taking if trouble breathing, throat tightness or swelling, trouble swallowing, dizziness, rapid heart rate, severe stomach symptoms
- Possibility of systemic (anaphylactic) reaction (lower risk than immunotherapy injections)
- Offer an EpiPen for home use

Short Ragweed Pollen Extract Ragwitek®

- Indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis confirmed by positive allergy testing
- Dose one tablet sublingual daily
- Start 12 weeks prior to season
- Ages 18 - 65
- Do not use in severe or uncontrolled asthma

Short Ragweed Pollen Extract Ragwitek®

- Side Effects
 - ◆ Throat irritation
 - ◆ Ear itching
 - ◆ Oral itching
 - ◆ Mouth tingling
 - ◆ Mouth edema
- Stop taking if throat tightness or swelling, trouble breathing, trouble swallowing, dizziness, rapid heart rate, severe stomach problems
- Possibility of systemic (anaphylactic) reaction (lower risk than immunotherapy injections)
- Offer an EpiPen for home use

Asthma & Allergy Pipeline



- SLIT – Dust mite or cat allergy
- Generic version of Advair – may be up to 8 generic versions in the pipeline, all using different devices
- 3M's Intelligent Control Inhaler (2016) – provides data on inspiratory flow, integrated patient instructions, profiles to help monitor disease progression
- Novartis' Breezhaler digital inhaler device integrated with smart phone
- Generic albuterol – expected by end of 2016 or in 2017
- New biologics: Anti-IgE antibodies, Anti-IL-13 antibodies and Anti-IL-13/Anti-IL-4 receptor antibodies – show real promise
- Triple therapy – ICS/LABA/LAMA

What is Success: How do we measure it and how do we get there?

- Begin therapy based on Severity
- Monitor and adjust therapy based on Control and Risk and Responsiveness to Therapy
- Use routine standardized multifaceted measures
- The goal of therapy is to achieve control
- Individualize therapy based on likelihood of response and patient needs, desires and goals

Questions?

- **Contact Information:**

- Phone: 616-464-4816

- E-mail: Karen.Meyerson@priorityhealth.com

- ◆ **Download the Guidelines at:**

- <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>

- ◆ **Download the Summary Report at:**

- <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf>