OUTPATIENT Asthma Management

BREATHE Conference
Allergy and Asthma Specialists PC
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March 15, 2019

Disclosures

- None

Outline

- Review the concepts of severity, control, impairment, & risk
  - Based on National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) 2007 as well as similar guidelines published by the Global Initiative for Asthma (GINA)
- Review age-based assessment & step therapy charts and apply with 6 clinical cases
- Review step-based medication options
- Review the FDA-approved biologics for treatment of moderate to severe persistent asthma

This Talk Will NOT Include

- Aspirin-exacerbated respiratory disease (AERD)
- Occupational asthma
- Chronic obstructive pulmonary disease (COPD
- Vocal cord dysfunction (VCD)
- Diagnostic procedures including pulmonary function tests (PFTs), methacholine challenge, fraction of exhaled nitric oxide (FENO)
- Inhaler technique
- Sulfite sensitivity or respiratory symptoms in food allergy

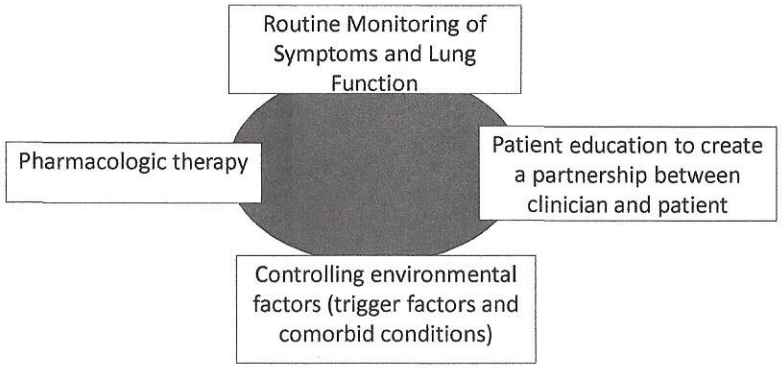
"Your breathing test results would be normal ... if you were 3'8" and 150 years old."

Background

- The most common serious chronic lung disease
- According to the CDC, 1 in 13 people have asthma.
- Estimated 334 million people affected by asthma worldwide
- Asthma accounts for
  - 14.2 million doctor's office visits yearly
  - 1.8 million ED visits yearly
  - 439,000 discharges from hospital inpatient care yearly
- Each day, 10 Americans die from asthma. In 2015, 3,615 people died from asthma. Many of these deaths are avoidable with proper treatment and care
- In the US alone, annual direct costs for asthma are estimated to be ~$50 billion

1. Global Asthma Network. The global asthma report 2014. Auckland, New Zealand: Global Asthma Network; 2014
2. Blaiss et al. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. Ann Allergy Asthma Immunol 119 (2017) 533–540.
3. CDC.gov [2018].

Components of Asthma Management



Goals of Asthma Treatment

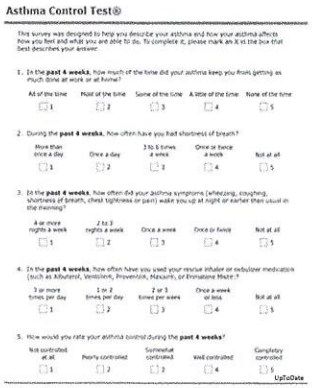
- Reduce IMPAIRMENT
  - The intensity and frequency of asthma symptoms and the degree to which the patient is limited by these symptoms.
- Reduce RISK
  - Adverse outcomes associated with asthma and its treatment

Impairment and Risk

Impairment (Current)	Risk (Future)
•Symptoms (day, night) •Rescue therapy •Activity •Lung function	•Exacerbations •Loss of lung function •Medication side effects

Principles of Monitoring Asthma Patients

- Assess symptoms
  - Impairment – assesses asthma control
    - Various validated questionnaires
      - ACT - range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control. An ACT score **>19** indicates well-controlled asthma
  - Risk – assesses risk for future exacerbatio
- Monitor pulmonary function
  - In office:
    - Spirometry
    - FeNO
  - At home:
    - Peak flow meter


Asthma Control Test®

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an X in the box that best describes your answer.

1. In the **past 4 weeks**, how much of the time did your asthma keep you from getting as much done at work or at home?

All of the time | Most of the time | Some of the time | A little of the time | None of the time
☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5

2. During the **past 4 weeks**, how often have you had shortness of breath?

More than once a day | Once a day | 3 to 6 times a week | Once or twice a week | Not at all
☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5

3. In the **past 4 weeks**, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week | 2 to 3 nights a week | Once a week | Once or twice | Not at all
☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5

4. In the **past 4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair®, or Primatene Mist®)?

3 or more times per day | 1 to 2 times per day | 2 or 3 times per week | Once a week or less | Not at all
☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5

5. How would you rate your asthma control during the **past 4 weeks**?

Not controlled at all | Poorly controlled | Somewhat controlled | Well controlled | Completely controlled
☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5

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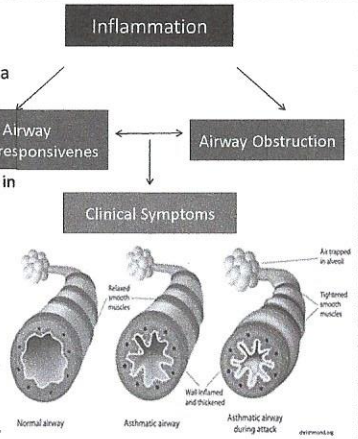
Principles of Monitoring Asthma Patients (Cont'd)

- Patient education
  - Asthma Action Plan, inhaler technique
- Controlling triggers and comorbid conditions
  - Aeroallergens at home, daycare, school, work
    - Evaluation by allergist
  - Irritants (e.g. tobacco smoke, wood smoke from fireplaces, perfumes, cleaning products, air pollutants)
  - Conditions we see commonly with asthma: COPD, GERD, obesity, OSA, chronic rhinosinusitis, vocal chord dysfunction, psychiatric comorbidities and stress
- Vaccinations
  - Yearly influenza vaccine recommended
  - Pneumococcal vaccine
    - Adults whose asthma is severe enough to require controller medication
    - Children with asthma who require chronic oral glucocorticoid therapy

1. Klemets P et al. Risk of invasive pneumococcal infections among working age adults with asthma. Thorax. 2010;65(8):698
2. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). www.ginasthma.org

Pharmacologic Treatment

- The mainstay of management in most patients with asthma
- Treatment is important in preventing:
  - Chronic airway inflammation that can progress over time to cause permanent structural changes in the airway wall associated with airflow obstruction
  - Irreversible airway obstruction appears to occur most often in those with longstanding, severe disease or a history of recurrent severe asthma exacerbations
- NAEPP EPR-3 recommends a <u>stepwise approach</u> to pharmacologic therapy.
  - These guidelines were intended to support, rather than dictate, care that is based upon the clinician's clinical judgment.
- The stepwise approach is based on <u>increasing medications until asthma is controlled</u>, and <u>decreasing medications when possible to minimize side effects</u>. Adjustment of the patient's management should be considered at every visit.



1. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Asthma Control and Severity

- The first step in determining appropriate therapy *for patients who are not already on a controller medication* is classifying the **severity** of the patient's asthma.
- For patients *already taking one or more controller medications*, treatment options are guided by an assessment of asthma **control** rather than asthma severity.

National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Asthma Severity

- Determined by considering the following factors:
  - Reported symptoms over the previous two to four weeks
  - Current level of lung function (PEFR or FEV_1 and FEV_1/FVC values)
  - Number of exacerbations requiring oral glucocorticoids in the previous year

Severity is based on the most severe element

Classifying asthma severity and initiating treatment in youths greater than or equal to 12 years of age and adults

Components of severity		Classification of asthma severity (≥12 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
Normal FEV_1/FVC: 8 to 19 years 85 percent; 20 to 39 years 80 percent; 40 to 59 years 75 percent; 60 to 80 years 70 percent	Nighttime awakenings	≤2x/month	3 to 4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80 percent predicted • FEV_1/FVC normal	• FEV_1 ≥80 percent predicted • FEV_1/FVC normal	• FEV_1 >50 but <80 percent predicted • FEV_1/FVC reduced 5 percent	• FEV_1 <50 percent predicted • FEV_1/FVC reduced >5 percent
Risk	Exacerbations requiring oral systemic glucocorticoids	0 to 1/year (see footnote)	≥2/year (see footnote)		
		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 FEV_1			
Recommended step for initiating treatment		Step 1	Step 2	Step 3	Step 4 or 5
		In two to six weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.		And consider short course of oral systemic glucocorticoids	

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Asthma Severity (ages 5-11)

Classifying asthma severity and initiating treatment in children 5 to 11 years of age

Components of severity		Classification of asthma severity (5 to 11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2 times/month	3 to 4 times/month	>1 time/week but not nightly	Often 7 times/week
	Short-acting $beta_2$ agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 ≥80% predicted • FEV_1/FVC >80%	• FEV_1 = 60 to 80% predicted • FEV_1/FVC = 75 to 80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic glucocorticoids	0 to 1/year (see footnote)	≥2/year (see footnote)		
		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 FEV_1			
Recommended step for initiating treatment		Step 1	Step 2	Step 3, medium dose-inhaled glucocorticoids option	Step 3, medium dose-inhaled glucocorticoids option, or Step 4
				And consider short course of oral systemic glucocorticoids	
		In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly			

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Asthma Severity (ages 0-4)

Classifying asthma severity and initiating treatment in children 0 to 4 years of age

Components of severity		Classification of asthma severity (0 to 4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1 to 2 times/month	3 to 4 times/month	>1 time/week
	Short-acting $beta_2$ agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic glucocorticoids	0 to 1/year	≥2 exacerbations in 6 months requiring oral systemic glucocorticoids, or ≥4 wheezing episodes/one year lasting >1 day AND risk factors for persistent asthma		
		Consider severity and interval since last exacerbation			
		Frequency and severity may fluctuate over time			
		Exacerbations of any severity may occur in patients in any severity category			
Recommended step for initiating treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic glucocorticoids	
		In 2 to 6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4 to 6 weeks, consider adjusting therapy or alternative diagnoses.			

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Asthma Predictive Index (API)

- The NHLBI guidelines 2007 suggest using the API to help determine when to use long-term control therapy in children < 4 years
- API:
  - At least 1 Major Criteria
    - Parental asthma
    - Physician diagnosis of eczema
    - Sensitization of aeroallergens
  - OR 2+ Minor Criteria
    - Sensitization to food
    - >4% peripheral eosinophils
    - Wheezing part from colds
- Longer term therapy should be initiated for any of the following scenarios:
  - At least 4 episodes of wheezing in the previous year that lasted at least 1 day and affected sleep + positive API
  - Required symptomatic treatment 2+ days a week for more than 4 weeks
  - Requiring oral steroids twice in 6 months
  - Consider adding during periods or seasons of previously documented risk (e.g. viral URI seasons)

Severity and Control

Severity	Control
•Intrinsic intensity of disease process	• Degree to which signs and symptoms are minimized due to therapy • Goals of therapy are met
Assessed to initiate therapy	Assessed to monitor and adjust therapy

Adjusting meds in patients already on controller therapy

- In patients already taking controller asthma therapy, medication should be adjusted according to **asthma control.**
- Control is assessed based on impairment over the past 2-4 weeks (by history or a validated questionnaire), current FEV_1 or peak flow, and estimates of risk.
  - In patients with well controlled asthma, medications can be continued unchanged or potentially reduced in step-wise fashion
  - In patients with poorly controlled asthma, treatment should be "stepped up" along the 6-step protocol
  - In patients with very poorly controlled asthma, it may be necessary to escalate therapy rapidly, then "step-down" again once good control is achieved
- Therapy should be reassessed at each visit, because the management of asthma is a dynamic process that changes in accordance with the patient's needs over time.

National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

What is considered good control?

- Daytime symptoms no more than 2x per week
- Nighttime symptoms no more than 2x per month.
- SABAs for relief of asthma symptoms should be needed < 3 days out of the week
- No interference with normal activity (preventative use of a SABA, such as prior to exercise, is acceptable even if used in this way on a daily basis).
- Lung function should remain normal or near-normal.
- Oral glucocorticoid courses and/or urgent care visits should be needed no more than once per year

National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Asthma Control (12+)

Assessing asthma control and adjusting therapy in youths greater than or equal to 12 years of age and adults

Components of control		Classification of asthma control (≥12 years of age)		
		Well-controlled	Not-well controlled	Very poorly controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1 to 3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80 percent predicted/personal best	60 to 80 percent predicted/personal best	<60 percent predicted/personal best
	Validated questionnaires			
	ATAQ	0	1 to 2	3 to 4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16-19	≤15
Risk	**Exacerbations requiring oral systemic glucocorticoids**	**0 to 1/year**	**≥2/year (see footnote)**	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	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.		
Recommended action for treatment		• Maintain current step • Regular followups every one to six months to maintain control • Consider step down if well controlled for at least three months	• Step up 1 step and • Reevaluate in two to six weeks • For side effects, consider alternative treatment options	• Consider short course of oral systemic glucocorticoids. • Step up 1 to 2 steps, and • Reevaluate in two weeks • For side effects, consider alternative treatment options

1. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm
2. Thomas A et al. Approaches to stepping up and stepping down care in asthmatic patients. J Allergy Clin Immunol. 2011 Nov;128(5):915-24; quiz 925-6. Epub 2011 Sep 8.

Asthma Control (ages 0-4 and 5-11)

Assessing asthma control in children 5 to 11 years of age

Components of control		Classification of asthma control (children 5 to 11 years of age)		
		Well controlled	Not well controlled	Very poorly controlled
Impairment	Symptoms	≤2 days/week, but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1 time/month	≥2 times/month	≥2 times/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function			
	FEV_1 or peak flow	>80% predicted personal best	60 to 80% predicted personal best	<60% predicted personal best
	FEV_1/FVC	>80%	75 to 80%	<75%
Risk	**Exacerbations requiring oral systemic glucocorticoids**	**0 to 1/year**	**≥2/year (see footnote)**	
		Consider severity and interval since last exacerbation		
	Treatment-related adverse effects	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.		

Assessing asthma control in children 0-4 years of age

Components of control		Classification of asthma control (children 0-4 years of age)		
		Well-controlled	Not-well controlled	Very poorly controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	**Exacerbations requiring oral systemic corticosteroids**	**0-1/year**	**2-3/year**	**>3/year**
	Treatment-related adverse effects	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.		

Stepwise Therapy (12+)

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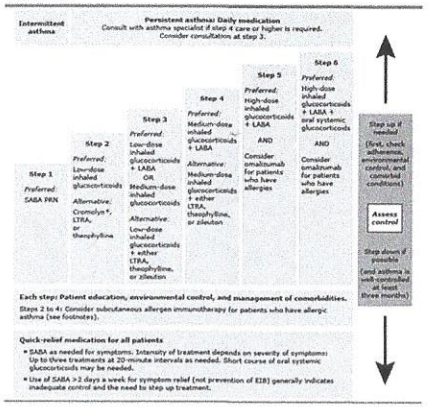
Stepwise approach for managing asthma in youths ≥12 years of age and adults



Stepwise Therapy (Children 0-11)

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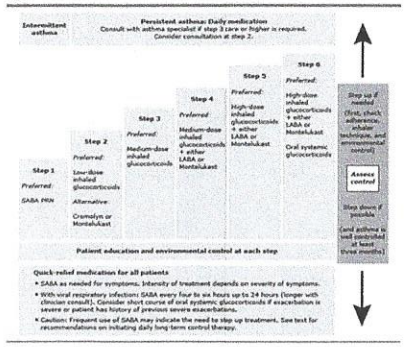
Stepwise approach for managing asthma in children 0 to 4 years of age



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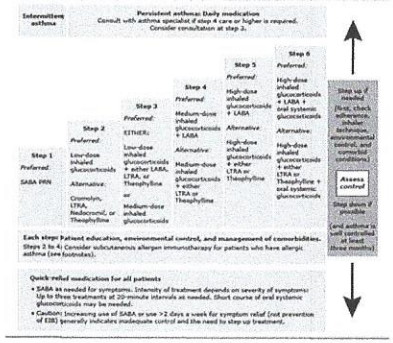
Stepwise approach for managing asthma in children 5 to 11 years of age



Asthma Medications - ICS (12+)

Estimated comparative daily doses for inhaled glucocorticoids in adolescents and adults

Drug	Low dose	Medium dose	High dose
Beclomethasone HFA (Qvar and Qvar Redimex products available in United States)*	80 to 160 mcg	>160 to 320 mcg	>320 mcg
40 mcg per puff	2 to 4 puffs	¶	¶
80 mcg per puff	1 to 2 puffs	3 to 4 puffs	>4 puffs
Beclomethasone HFA[A] (Qvar product available in Canada, Europe, and elsewhere)	100 to 200 mcg	>200 to 400 mcg	>400 mcg
50 mcg per puff	2 to 4 puffs	¶	¶
100 mcg per puff	1 to 2 puffs	3 to 4 puffs	>4 puffs
Budesonide DPI (Pulmicort Flexhaler product available in United States)*	180 to 360 mcg	>360 to 720 mcg	>720 mcg
90 mcg per inhalation	2 to 4 inhalations	¶	¶
180 mcg per inhalation	1 to 2 inhalations	3 to 4 inhalations	>4 inhalations
Budesonide DPI[A] (Pulmicort Turbuhaler product available in Canada, Europe, and elsewhere)	200 to 400 mcg	>400 to 800 mcg	>800 mcg
100 mcg per inhalation	2 to 4 inhalations	¶	¶
200 mcg per inhalation	1 to 2 inhalations	3 to 4 inhalations	¶
400 mcg per inhalation	1 inhalation	2 inhalations	>2 inhalations
Ciclesonide HFA (Alvesco product available in United States, Europe, and elsewhere)*	80 to 160 mcg	>160 to 320 mcg	>320 mcg
80 mcg per puff	1 to 2 puffs	3 to 4 puffs	¶
160 mcg per puff	1 puff	2 puffs	>2 puffs
Ciclesonide HFA[A] (Alvesco product available in Canada)	100 to 200 mcg	>200 to 400 mcg	>400 mcg
100 mcg per puff	1 to 2 puffs	3 to 4 puffs	¶
200 mcg per puff	1 puff	2 puffs	>2 puffs
Fluticasone HDI (Arnuity product available in United States)*	100 mcg	>100 to 200 mcg	Insufficient data
50 mcg per puff	2 puffs	4 puffs	Insufficient data
Fluticasone propionate HFA (Flovent HFA product available in United States)*	88 to 220 mcg	>220 to 440 mcg	>440 mcg
44 mcg per puff	2 to 5 puffs	¶	¶
110 mcg per puff	1 to 2 puffs	3 to 4 puffs	¶
220 mcg per puff	∞	2 puffs	>2 puffs

Asthma Medications – ICS/LABA (12+)

Usual doses of combination inhaled glucocorticoids and long-acting beta-agonists for the treatment of asthma in adolescents age 12 and older and adults

Medication	Low dose	Medium dose	High dose
Budesonide-formoterol HFA (Brand name: Symbicort)			
80 mcg-4.5 mcg 160 mcg-4.5 mcg	2 puffs twice a day	2 puffs twice a day	
Fluticasone furoate-vilanterol DPI (Brand name: Breo Ellipta)*			
NOTE: Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than fluticasone propionate inhalers. Thus, fluticasone furoate is administered at a lower daily dose and used only **once** daily.			
100 mcg-25 mcg 200 mcg-25 mcg		1 inhalation once daily	1 inhalation once daily
Fluticasone propionate-salmeterol DPI (Brand name: Advair Diskus)			
100 mcg-50 mcg 250 mcg-50 mcg 500 mcg-50 mcg	1 inhalation twice a day	1 inhalation twice a day	1 inhalation twice a day
Fluticasone propionate-salmeterol HFA (Brand name: Advair HFA)			
45 mcg-21 mcg 115 mcg-21 mcg 230 mcg-21 mcg	2 puffs twice a day	2 puffs twice a day	2 puffs twice a day
Fluticasone propionate-salmeterol DPI (Brand name: AirDuo RespiClick)[¶]			
55 mcg-14 mcg 113 mcg-14 mcg 232 mcg-14 mcg	1 inhalation twice a day 1 inhalation twice a day	1 inhalation twice a day	1 inhalation twice a day
Mometasone-formoterol HFA (Brand name: Dulera)			
100 mcg-5 mcg 200 mcg-5 mcg		2 puffs twice a day	2 puffs twice a day

Do not exceed the maximum number of inhalations/puffs per day listed in the table due to the risk of toxicity from an excess dose of long acting beta-agonist (ie, salmeterol, formoterol, or vilanterol). Brand names and dose per puff or per inhalation of commercially available fixed dose combinations are according to United States licensed product information. Consult local product information before use.

Asthma Medications – ICS (0-11)

Estimated comparative daily doses for inhaled glucocorticoids in children

Drug	Low daily dose		Medium daily dose		High daily dose	
	Child 0 to 4	Child 5 to 11	Child 0 to 4	Child 5 to 11	Child 0 to 4	Child 5 to 11
Beclomethasone HFA 40 or 80 mcg/puff	NA	40 mcg/puff - 1 to 2 puffs twice per day	NA	40 mcg/puff - 2 to 4 puffs twice per day 80 mcg/puff - 1 to 2 puffs twice per day	NA	80 mcg/puff - 3 to 4 puffs twice per day
Budesonide DPI* (breath activated) 90 or 180 mcg/inhalation	NA	90 mcg/inhalation - 1 to 2 inhalations twice per day	NA	180 mcg/inhalation - 1 to 2 inhalations twice per day	NA	180 mcg/inhalation - 3 to 4 inhalations twice per day
Budesonide nebulization suspension[¶] 0.25 mg/2 mL, 0.5 mg/2 mL, or 1 mg/2 mL	0.25 to 0.5 mg once daily or as 2 divided doses	0.5 mg once daily or as 2 divided doses	0.75 to 1 mg once daily or as 2 or 3 divided doses	1 mg once daily or as 2 divided doses	1.25 to 2 mg once daily or as 2 divided doses	2 mg once daily or as 2 divided doses
Ciclesonide HFA[Δ] 80 or 160 mcg/puff	NA	80 mcg/puff - 1 to 2 puffs once daily	NA	80 mcg/puff - 3 to 4 puffs once daily	NA	80 mcg/puff - 5 to 6 puffs once daily or as 2 divided doses 160 mcg/puff - 3 puffs once daily or as 2 divided doses
Flunisolide HFA (built-in spacer)[◊] 80 mcg/puff	NA	80 mcg/puff - 1 puff twice per day[◊]	NA	80 mcg/puff - 2 puffs twice per day[◊]	NA	Not recommended[◊]
Fluticasone HFA[¥] 44, 110, or 220 mcg/puff	44 mcg/puff - 2 puffs twice per day[¥]	44 mcg/puff - 1 to 2 puffs twice per day	44 mcg/puff - 2 to 4 puffs twice per day 110 mcg/puff - 1 puff vs AM and 2 puffs vs PM	44 mcg/puff - 2 to 4 puffs twice per day 110 mcg/puff - 1 puff vs AM and 2 puffs vs PM	110 mcg/puff - 2 puffs twice per day 220 mcg/puff - 1 puff twice per day	110 mcg/puff - 2 puffs twice per day 220 mcg/puff - 1 puff twice per day
Fluticasone DPI (breath activated)[¥] 50, 100, or 250 mcg/inhalation	NA	50 mcg/inhalation - 1 to 2 inhalations twice per day	NA	50 mcg/inhalation - 1 to 4 inhalations twice per day 100 mcg/inhalation - 1 inhalation vs AM and 2 inhalations vs PM to 2 inhalations twice per day	NA	100 mcg/inhalation - 2 inhalations vs AM and 2 inhalations vs PM 250 mcg/inhalation - 1 inhalation twice per day
Mometasone aerosol DPI (breath activated)* 110 or 220 mcg/inhalation	NA	110 mcg/inhalation - 1 inhalation once daily	NA	110 mcg/inhalation - 1 to 3 inhalations once daily	NA	110 mcg/inhalation - 4 inhalations once daily or 2 inhalations twice per day 220 mcg/inhalation - 2 inhalations once daily or 1 inhalation twice per day

Other Asthma Medications (0-11)

Usual doses for long-term asthma controller medications other than inhaled glucocorticoids in children*

Medication	Dose form	0 to 4 years	5 to 11 years	Comments
Leukotriene receptor antagonists (LTRAs)[¶]				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg once daily at bedtime (1 to 5 years of age)	5 mg once daily at bedtime (6 to 14 years of age)	When LTRA treatment is indicated, montelukast is preferred.
Zafirlukast	10 mg tablet	Safety and efficacy not established	10 mg twice per day on empty stomach	Zafirlukast has potential drug interactions and a small risk of hepatotoxicity. Food decreases bioavailability of zafirlukast; take at least one hour before or two hours after meals.
Combined inhaled glucocorticoids and long-acting beta agonists (LABAs)[¶]				
Fluticasone-salmeterol	DPI 100 mcg/50 mcg MDI 45 mcg/21 mcg	Safety and efficacy not established	One inhalation twice a day	Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery of DPI.
Budesonide-formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established	Two puffs twice per day One to two puffs twice per day	Do not exceed dose shown. Onset of formoterol is similar to albuterol. There have been no clinical trials in children <4 years of age. Do not exceed dose shown.
Systemic glucocorticoids				
Methylprednisolone Prednisolone Prednisone	For detail, refer to Lexicomp Drug specific monographs included with UpToDate®	0.25 to 2 mg/kg orally per day or every other day given in the morning. Titrate to the lowest acceptable dose that maintains control.	0.25 to 2 mg/kg orally per day or every other day given in the morning. Titrate to the lowest acceptable dose that maintains control.	**(Applies to all three glucocorticoids)** Due to their toxic effects, systemic glucocorticoids should be used only rarely for long-term control of asthma, ie, in those few patients with poorly-controlled severe persistent asthma despite compliance with maximized ICS and other pharmacologic and preventive therapies. Refer to topic. The use and dosing of systemic glucocorticoids for the treatment of acute asthma exacerbations is reviewed elsewhere. Refer to separate topic reviews on acute asthma exacerbation in children, emergency department, and inpatient management.
Chromones				
Cromolyn sodium (sodium cromoglycate)	5 mg/puff CFC free MDI (not available in the United States)[◊] 20 mg/ampule solution for nebulization	Safety and efficacy not established 20 mg four times per day Safety and efficacy not established in children aged <2 years	Two puffs four times per day 20 mg four times per day	Less effective than ICS in children. Add-on to ICS is not recommended. Refer to topic. Four to six week trial may be needed to determine maximum benefit. May cause bronchospasm. Premedication with bronchodilator may be needed. Use of spacer device may substantially decrease amount of drug delivered. Once control is achieved, the frequency of dosing may be reduced.
Nedocromil	2 mg/puff CFC free inhaler (not available in the United States)[◊]	Safety and efficacy not established in children aged <6 years	Two puffs four times per day	
Anti-IgE therapy: Refer to separate topic on anti-IgE therapy				

Asthma Medications – Anti-Leukotrienes

Usual doses of antileukotriene agents in the management of persistent asthma

Medication	Preparations	Infant and small child	Pediatric	Adolescent and adult
Montelukast	Granules: 4 mg per packet Chewable tablets: 4 mg, 5 mg Tablet: 10 mg	12 months* to 5 years: 4 mg granules or chewable tablet once daily in evening	6 to 14 years: 5 mg chewable tablet once daily in evening	≥15 years and adult: 10 mg tablet once daily in evening
Zafirlukast[¶]	Tablets: 10 mg, 20 mg	(Not studied)	5 to 11 years: 10 mg twice per day	≥12 years and adult: 20 mg twice per day
Zileuton[¶]	Immediate-release tablet: 600 mg Extended-release tablet: 600 mg	(Not studied)	(Not studied)	≥12 years and adult: • Immediate release: 600 mg four times per day • Extended release: 1200 mg twice per day
Pranlukast[Δ]	Capsules: 112.5 mg, 225 mg Granules: 50 mg, 70 mg, 100 mg per packet	24 months to 5 years: 7 to 10 mg/kg granules per day in two divided doses	6 to 11 years: 7 to 10 mg/kg per day granules in two divided doses (maximum 225 mg twice per day)	≥12 years and adult: 225 mg twice per day

Asthma Medications Resource

"That's a puffer. If you want to blow a house down, you'll also need a huffer."

"See, son? Daddy's company makes inhalers to help people with asthma."

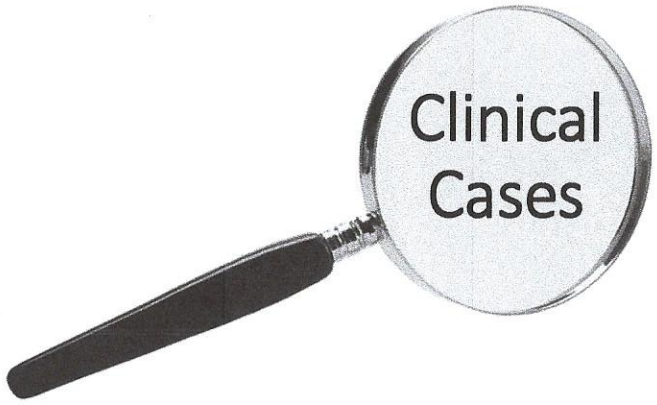
https://www.aaaai.org/conditions-and-treatments/drug-guide/inhaled-corticosteroids

Lists the ICS and ICS/LABAS and includes generic and brand names, ages, dosages, product links, and photo of inhalers.

Historical Factoids

- Roman doctors described asthma as gasping and the inability to breathe without making noise.
- In Homer's *Odyssey*, he mentions Odysseus and Diomedes are "*asthmainonte*" after chasing after a soldier from Troy.
- Pliny the Elder (~ 50 AD) observed that pollen was a source of respiratory difficulty and recommended the use of "ephedra" (forerunner of ephedrine) in red wine as an asthma remedy.
  - Though he also suggested that drinking the blood of wild horses and eating 21 millipedes soaked in honey could help...
- In South America in the 1500s, the Incans treated asthma with a cocaine-like dried leaf.
- In the 1800's, arsenic was prescribed for respiratory conditions.

1. Saunders KB. Origin of the word asthma. Thorax 1993 Jun; 48(6):647.
2. C. Plinius Secundus. Naturelle historie.
3. Hughes MF et al. Arsenic Exposure and Toxicology: A Historical Perspective. Toxicol Sci. 2011 Oct; 123(1): 305–332.

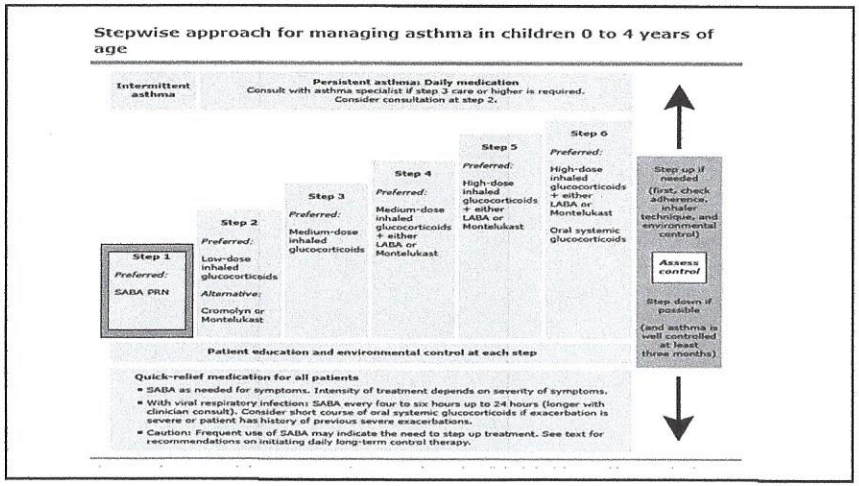


Clinical Case #1

An 4 year old male presents to your office for evaluation for wheezing. He has no significant daytime or nighttime symptoms or with activity. His pediatrician prescribed an albuterol nebulizer that parents report he has rarely used. His parents have used it in the setting of cold weather and viral infections, which they feel are his only triggers. He has had no ED visits, hospitalizations, or required oral steroids over the last year. On exam, his lungs are clear.

WELL CONTROLLED MILD **INTERMITTENT** ASTHMA

- Daytime symptoms occurring ≤ 2 days per week
- ≤2 nocturnal awakenings per month
- Use of SABA ≤2 days per week
- No interference with normal activities between exacerbations
- (FEV1 measurements between exacerbations that are consistently within the normal range)
- (FEV1/FVC ratio between exacerbations that is normal (based on age-adjusted values))
- 0-1 exacerbations requiring oral glucocorticoids per year



Mild Intermittent Asthma Treatment

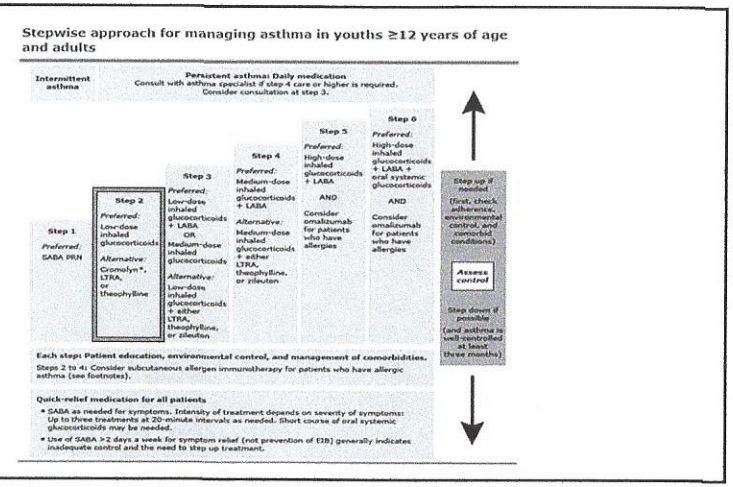
- Patients with mild intermittent asthma are best treated with a quick-acting inhaled beta-2-selective adrenergic agonist, taken as needed for relief of symptoms
- Patients for whom triggering of asthmatic symptoms can be predicted (eg, exercise-induced bronchoconstriction) are encouraged to use their inhaled beta agonist approximately 10 minutes prior to exposure in order to prevent the onset of symptoms.
- Assess control at subsequent visits and step up if needed
- Review inhaler technique

Clinical Case #2

A 24-year-old woman is evaluated for increasing asthma symptoms. Her symptoms now require her to *use her as-needed albuterol inhaler two to three times per week*, and she has been *waking up at night at least once a week with asthma symptoms that require her inhaler*. She is still *able to perform most of her daily activities*, including regular exercise, if she uses albuterol for prevention. She is allergic to house dust mites, ragweed, grass, trees, and cats.

- On physical examination, vital signs are normal. Pulmonary examination is normal with no wheezing. Spirometry shows an FEV_1 of 85% of predicted and an FEV_1/FVC ratio of 80% of predicted.
- MILD **INTERMITTENT** ASTHMA that is NOT WELL CONTROLLED -> MILD **PERSISTENT** ASTHMA
  - Symptoms > twice weekly (but less than daily)
  - Approximately 3-4 four nocturnal awakenings per month due to asthma
  - Use of SABAs to relieve symptoms ≥ 2 days out of the week (but not daily)
  - Minor interference with normal activities
  - FEV1 measurements within normal range (≥80 percent of predicted normal) and normal FEV1/FVC ratio
  - ≥2 exacerbations requiring oral glucocorticoids per year

From MKSAP 16



Mild Persistent Asthma Treatment

- Add a low-dose inhaled corticosteroid
- Alternatives to ICS include a leukotriene receptor antagonist or theophylline
- LABA should be added if medium-dose ICS therapy fails to control symptoms
- Scheduled use of albuterol is not recommended, because it might mask ongoing airway inflammation and the need to provide anti-inflammatory therapy with ICS
- Refer for allergy evaluation
- Update asthma action plan
- Assess control at subsequent visits and step up (or down) as needed
- Review inhaler technique

Clinical Case #3

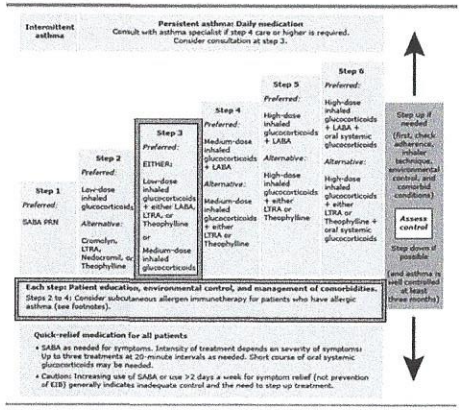
A 10 year old male presents to your office for asthma follow up. His last office visit was 3 years ago. Mom feels he has been more short of breath and wheezes more than usual. He feels he has symptoms almost daily requiring his rescue inhaler. Mom has also noticed some coughing 2-3 nights a week that wakes him up from sleep. Mom has noticed that occasionally his symptoms interfere with his soccer practice. He is on a low dose ICS 2 puffs twice daily and does not miss any doses. Over the last year, he has had 2 ED visits for asthma flares in the setting of colds and each visit was prescribed a short course of oral steroids.

- In the office, his spirometry shows an FEV1/FVC of 75%.
- He also has significant seasonal allergic rhinitis symptoms (sneezing, itchy and watery eyes, runny nose) worst in the spring and fall. There are no pets at home.

Moderate Persistent Asthma – NOT Well Controlled

- Daily symptoms of asthma
- Nocturnal awakenings more than once per week
- Daily need for SABAs for symptom relief
- Some limitation in normal activity
- FEV1 between 60-80% of predicted
- FEV1/FVC below normal

Stepwise approach for managing asthma in children 5 to 11 years of age



Moderate Persistent Asthma Treatment

- Increase ICS to medium dosed ICS OR add LABA, LTRA to low dose ICS
- Refer to allergist for skin testing -> may be a good candidate for allergen immunotherapy
- Review inhaler technique
- Monitor growth curve while on inhaled steroids
- Review asthma action plan
- In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.

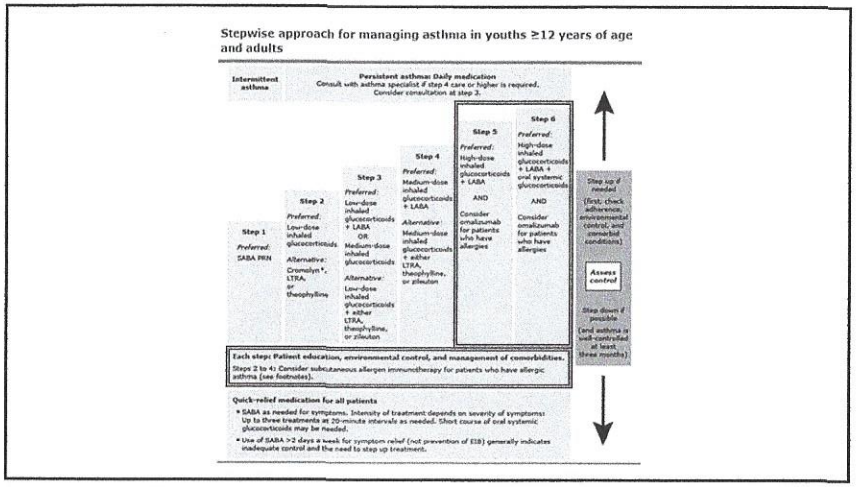
Clinical Case #4

A 35 year old woman is sent from her PCP's office for evaluation of asthma and allergies. She reports she feels wheezy and short of breath daily throughout the day. Walking down the street and climbing even a flight of stairs have been difficult. She feels she can no longer go to the gym because of her symptoms. She also has almost daily nighttime symptoms as well. She takes a high dose ICS/LABA, ipratropium, and montelukast and generally does not miss any doses but feels she still requires her rescue inhaler 1-3 times a day. She has no cardiac comorbidities or history of hypercoagulable disorder.

- She reports 2 hospitalizations for asthma within the last 5 years but has never had to be intubated. So far this past year, she has had 4 exacerbations requiring oral steroids.
- In office her FEV1/FVC is 58%.
- She reports significant seasonal and perennial allergic rhinitis symptoms including symptoms around cats and dogs. She lives in the city and has 2 cats at home, which she cannot get rid of because there are mice in the house. She takes cetirizine and uses a steroid nose spray year round.

Poor Control of Severe Persistent Asthma

- Symptoms of asthma throughout the day
- Nocturnal awakenings nightly
- Need for SABAs for symptom relief several times per day
- Extreme limitation in normal activity
- FEV1 <60 percent of predicted and FEV1/FVC below normal

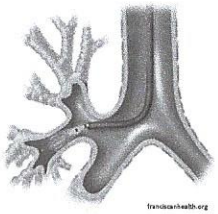


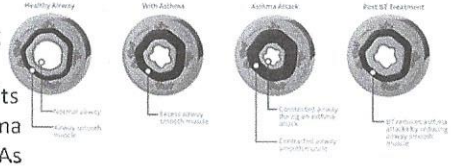
Severe Persistent Asthma Treatment

- Strongly consider biologic and appropriate obtain lab work (more on this soon)
- When lung function improves, aeroallergen skin testing evaluation; if unable, can do blood testing
- Discuss environmental control measures
- Consider pulmonary evaluation for bronchial thermoplasty (next slide)
- Review inhaler technique
- Asthma flare plan
- Regular follow up

Bronchial Thermoplasty

- Thermal energy applied via a special catheter introduced via a fiberoptic bronchoscope to impair bronchial smooth muscle contractility
- Criteria for BT
  - Poorly controlled asthma despite high dose ICS/LABA, nonsmoker for ≥1 year, FEV_1 ≥60 percent of predicted, no history of a life-threatening exacerbation, <3 hospitalizations in the last year, and willingness to accept the risk of an asthma exacerbation requiring hospitalization as a consequence of the procedure
- The FDA has approved marketing of Alair Bronchial Thermoplasty System for the treatment of adults (≥18 years old) with severe asthma not well-controlled with ICS/LABAs





1. Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343.

Clinical Case #5

A 15 year old girl with a history of asthma diagnosed since childhood presents to you for evaluation of progressive symptoms despite treatment.

- She reports symptoms of shortness of breath and chest tightness. She takes Advair 230-21mcg HFA two puffs twice daily with a spacer and Flovent 110mcg 2 puffs twice daily and Singulair. She reports she has not missed any doses of medications. She uses the correct technique. Despite this medication regimen, she reports using albuterol 1-2 times daily. Almost immediately after 1 puff of albuterol, she reports immediate improvement in her symptoms. She has not had any ED visits, hospitalizations, or required oral steroids over the last year. There is no interference with sports or activity. She reports no major nighttime symptoms.
- She has a history of anxiety and depression and sees a psychiatrist and counselor. She was recently started on fluoxetine. She reports significant stress from school.
- Her allergic rhinitis symptoms are mild and generally under control until she is exposed to any animals. She takes azelastine and fluticasone nose sprays with correct technique as well as cetirizine daily. There are no pets at home.
- She has no personal or family history of cardiac disease or hypercoagulable disorders.
- On exam, she is a well-appearing young woman, normal BMI, VSS, speaking in full sentences. Her lungs are clear. Her spirometry is non-obstructive. She has had comprehensive PFTs done by pulmonary a year ago that were normal as well as positive methacholine challenge that confirms the diagnosis of asthma.

Next Steps

- Reconciling normal objective findings with abnormal subjective symptoms
  - No major nighttime symptoms, no symptoms with exertion
  - Albuterol works immediately
- Use a peak flow meter whenever she feels she needs her rescue inhaler and record numbers -> trial off Flovent
  - Discussed if in green zone, this means no obstruction and does not acutely need albuterol; if symptoms worsen or in red zone after stopping Flovent, discussed restarting
- Spirometry at following office visit was normal again and PEF was persistently in the green zone -> stepped down on Advair
- Continue regular follow up with psychiatrist and counselor
- Follow up during pollen season, if doing well, can maybe step down from ICS/LABA to ICS

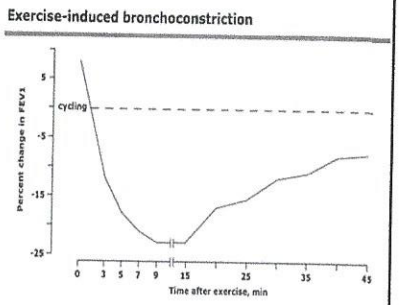
Clinical Case #6

A 16 year old male presents to you for evaluation of chest tightness, shortness of breath, and occasional cough that he feels begins within a few minutes into exercise and worsens about 15 minutes into activity. He would like to continue to be able to participate in after school sports. Apart from with exercise, he has no symptoms.

- On exam he is a well-appearing male. His lungs are clear. He has a normal FEV1/FVC on spirometry.

Exercise-Induced Bronchoconstriction (EIB)

- Bronchoconstriction begins by three minutes after exercise, generally peaks within 10 to 15 minutes, and resolves by 60 minutes
- DDx: vocal cord dysfunction, exercise-induced laryngomalacia, exercise-induced anaphylaxis, exercise-associated reflux
- Diagnosed clinically based on the combination of clinical symptoms (eg, exercise-related symptoms of dyspnea, cough, or wheeze) and demonstration of reversible airflow limitation in response to exercise challenge
- Exercise challenge test is the most direct and preferred way to establish a diagnosis of EIB
  - 6-10 minutes on treadmill to raise HR by 80-90% of predicted maximum
  - Positive test = FEV1 decreases by ≥ 10%



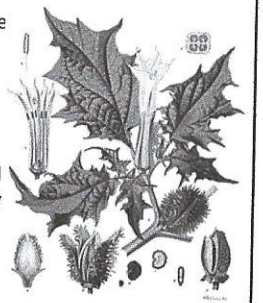
EIB Treatment

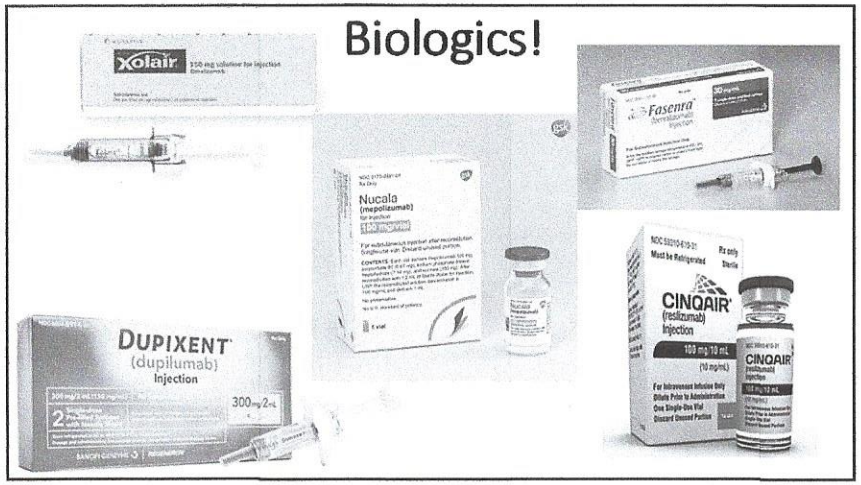
- Major goal is to ensure that exercise is not avoided by patients with EIB and they should exercise as much as desired
  - Athletes have won Olympic medals and played professional sports in spite of symptomatic asthma.
- First line for quick relief and preventative treatment is a SABA; 2 puffs are generally sufficient; occasionally four puffs are needed.
  - Ipratropium is generally not used for quick relief as bronchodilation is delayed (onset at 15 minutes and peak at 1 to 2 hours) compared with SABAs. Cromolyn sodium is not effective for quick relief.
- Patients who exercise for 3+ hours or more than once a day represent a challenge because use of SABA multiple times a day is likely to lead to tachyphylaxis
  - Thus, for patients who would require regular, daily dosing of a SABA, an ICS or LTRA is recommended
- What if SABA is not enough?
  - Review inhaler technique
  - When EIB is refractory to premedication with a SABA, poor asthma control is often the cause. The most effective method of achieving asthma control involves adding an ICS
- Interesting Fact:
  - Inhaled glucocorticoids are permitted by the WADA and do not need a Therapeutic Use Exception. Systemic glucocorticoids are prohibited in competition, and a Therapeutic Use Exception may need to be filed for use outside of competition. Leukotriene receptor antagonists (montelukast, zafirlukast) and omalizumab are permitted agents.

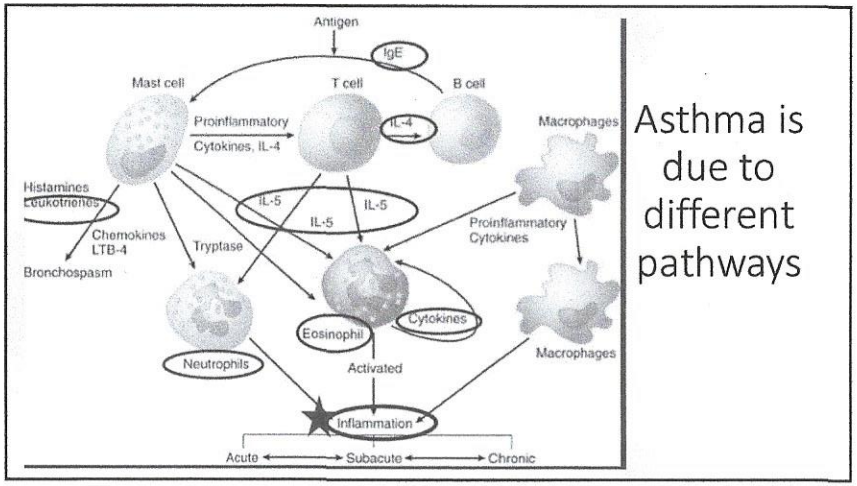
WORLD ANTI-DOPING AGENCY

Historical Factoids

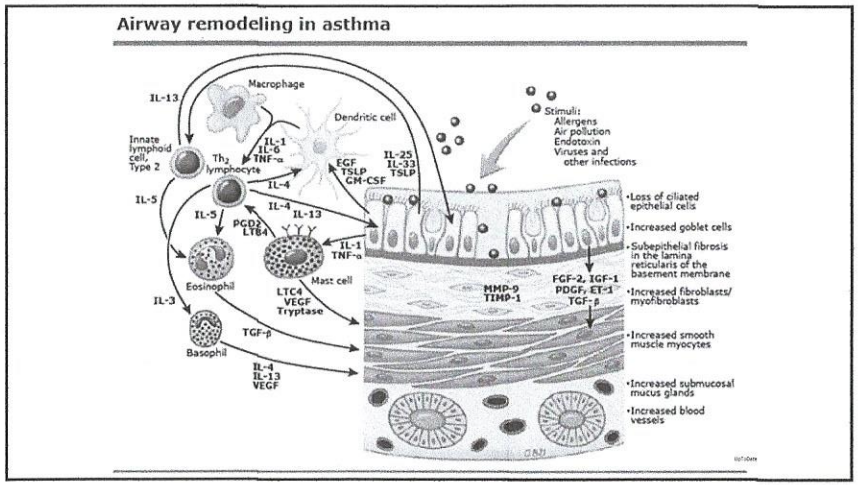
- When Alexander the Great invaded India (~327BC), he found that people were smoking the herb *Stramonium* was used to relax the lungs via its anticholinergic properties (similar to ipratropium and tiotropium).
- By 100 A.D., in ancient India, dried and crushed *Stramonium* was stuffed into pipes. The smoke was inhaled by asthmatics to obtain mild relief.
- In 1801, this treatment made its way to Europe and the U.S., and this created a craze that lasted until the 1950s.







Asthma is due to different pathways



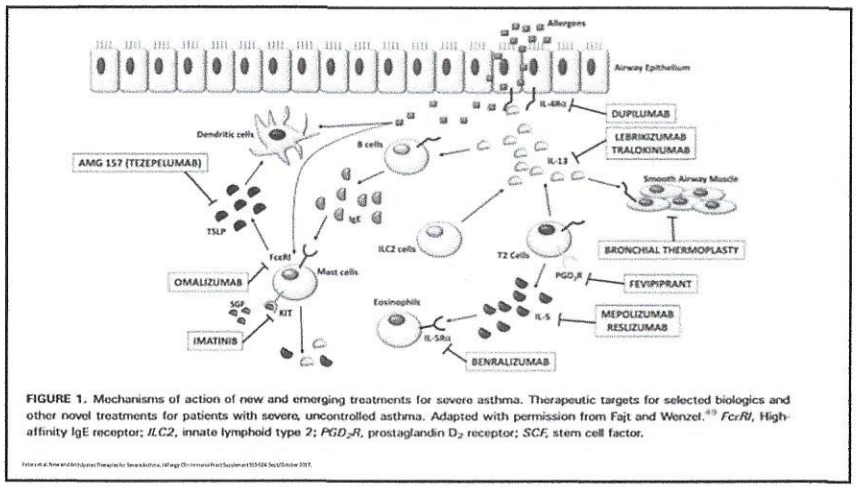
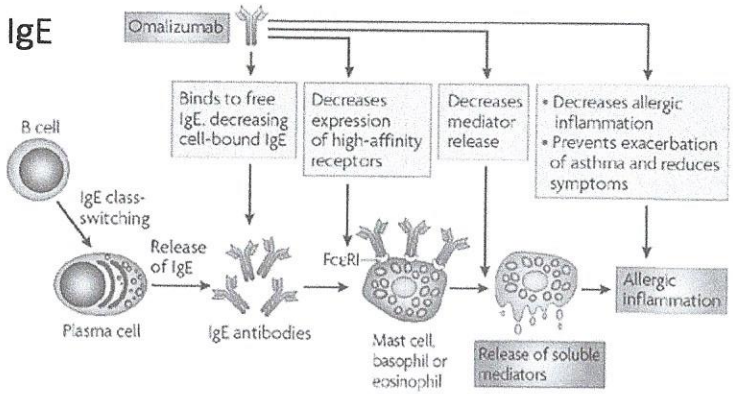


FIGURE 1. Mechanisms of action of new and emerging treatments for severe asthma. Therapeutic targets for selected biologics and other novel treatments for patients with severe, uncontrolled asthma. Adapted with permission from Fajt and Wenzel.[49] *FcεRI*, High-affinity IgE receptor; *ILC2*, innate lymphoid type 2; *PGD$_2$R*, prostaglandin D$_2$ receptor; *SCF*, stem cell factor.

Anti IgE



Anti IL-5

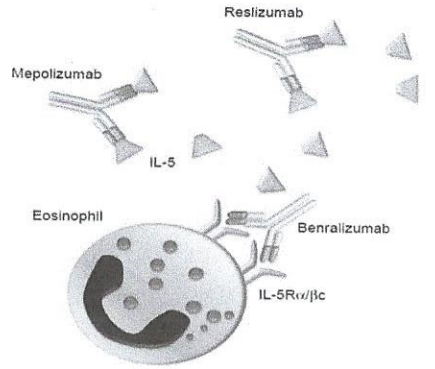
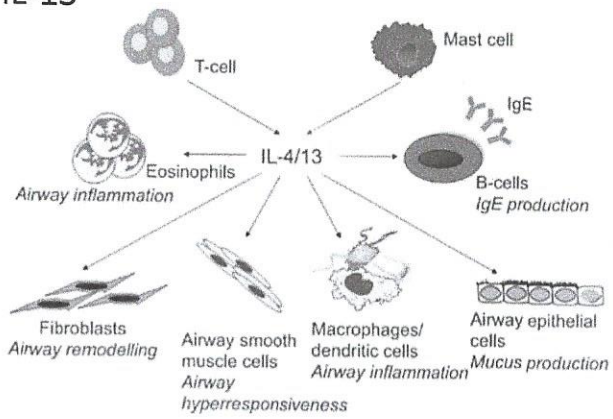


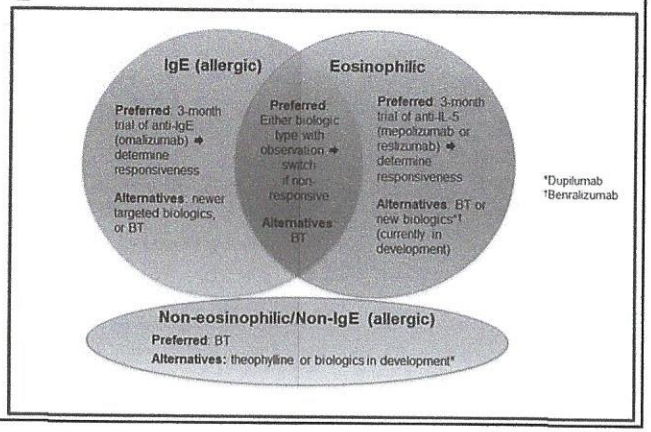
Figure 2 Anti-IL-5/IL-5R biologic therapies.
Notes: Monoclonal antibodies aimed to inhibit eosinophil functions include mepolizumab and reslizumab, which bind to and neutralize IL-5, as well as benralizumab, which targets and blocks IL-5Rα.

Anti IL-4 and IL-13



Agent	Target	FDA Approved Age	Labs Required	Route	Dose & Interval	Adverse Effects	Also Approved For
omalizumab (Xolair)	IgE	6+ years	--IgE 30-700 in US (30-1500 in Europe) --Sensitivity to perennial allergen	Sub-Q	Based on weight and IgE level (max 375mg every 2 weeks)	Local site reaction Anaphylaxis	CIU
mepolizumab (Nucala)	IL-5	12+ years	AEC 150+	Sub-Q	100mg every 4 weeks	Local site reaction Herpes zoster	EGPA
benralizumab (Fasenra)	IL-5 R alpha; EP apoptosis via NK cells	12+ years	AEC 300+	Sub-Q	30mg every 4 for first 3 doses; then every 8 weeks	Headache, fever	
reslizumab (Cinqair)	IL-5	18+	AEC 400+	IV	3mg/kg every 4 weeks	Anaphylaxis 0.3% (Black box warning) Transient increase in CPK	
dupilumab (Dupixent)	IL-4R alpha	12+ years	None in studies*	Sub-Q	2 doses: 200mg or 300mg every 2 weeks Home administration	Transient eosinophilia Injection site reactions Keratitis, conjunctivitis	Eczema

Which biologic do I choose?

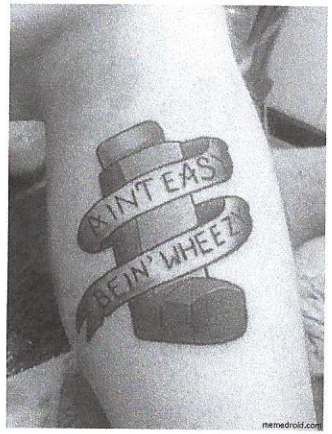


Other Biologics in the Pipeline

- Anti-TSLP (tezepelumab)
  - In phase III trials as of October 2018
  - SC injection
- Anti- IL-13 (tralokinumab and lebrikizumab)
  - IL-13 important in mucus hypersecretion and bronchial hyperresponsiveness
  - In phase II and III trials
  - SC injections
- Pitakinra
  - Recombinant IL-4 that is anti-IL-4 and IL-13
  - Targets T lymphocyte differentiation, IgE upregulation, mucus hypersecretion
  - Completed phase II trials, entering phase III trials
  - Inhalation > SC
- Anti IL-33, Anti- IL-31

When to refer?

- Both pulmonologists and allergists/immunologists have specialty training in asthma care. Referral for consultation or co-management is recommended when any of the following circumstances arise
  - The patient has experienced a life-threatening asthma exacerbation or has required frequent hospitalizations
  - Asthma is not controlled after three to six months of active therapy and appropriate monitoring
  - The patient appears unresponsive to therapy
  - The diagnosis of asthma is uncertain
  - Other conditions are present which complicate management (nasal polyposis, chronic sinusitis, severe rhinitis, allergic bronchopulmonary aspergillosis, COPD, vocal cord dysfunction, etc)
  - Additional diagnostic tests are needed (skin testing for allergies, bronchoscopy, complete pulmonary function tests)
  - Patient may be a candidate for allergen immunotherapy
  - Patient is a potential candidate for therapy with biologics or bronchial thermoplasty.

Conclusions

- The goal for therapy is to control asthma by:
  - Reducing impairment
  - Reducing risk
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains
- Discuss compliance and technique
- Biologics are the new frontier in allergic/atopic asthma
- Monitoring and follow-up is essential