Asthma: A Breathless Update

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Learning Objectives

1. Use evidence-based criteria to order and interpret appropriate tests for asthma.
2. Analyze environmental triggers for asthma with patients and select factors to reasonably avoid or control them.
3. Develop system-wide interventions that promote patient adherence to long-term management of chronic asthma.
4. Collaborate with asthma patients to develop an asthma action plan that encourages adherence.

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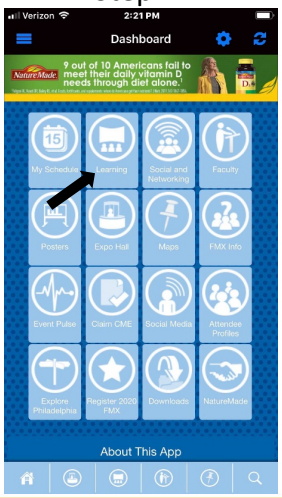
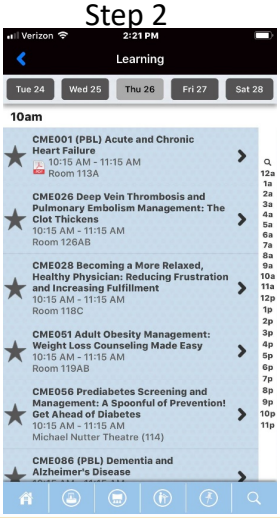
Audience Engagement System

Step 1



Step 2



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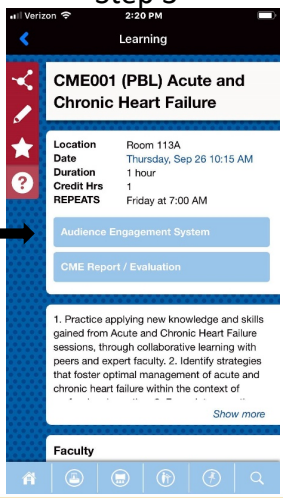

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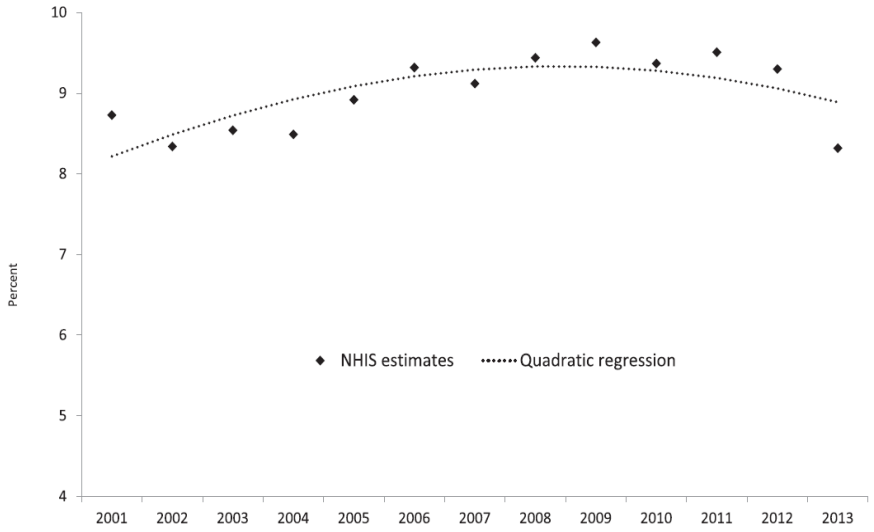
Abbreviations

- SABA: short-acting beta agonist
  - i.e.: albuterol
- LABA: long-acting beta agonist
  - i.e.: salmeterol, formoterol
- ICS: inhaled corticosteroid
  - i.e.: fluticasone, budesonide
- LABA/ICS: salmeterol/fluticasone (Advair), formoterol/budesonide (Symbicort)
- LTRA: leukotriene receptor antagonist
  - i.e.: montelukast (Singulair), zafirlukast (Accolate), zileuton (Zyflo)
- LAMA: long-acting muscarinic antagonist
  - i.e.: tiotropium bromide (Spiriva)

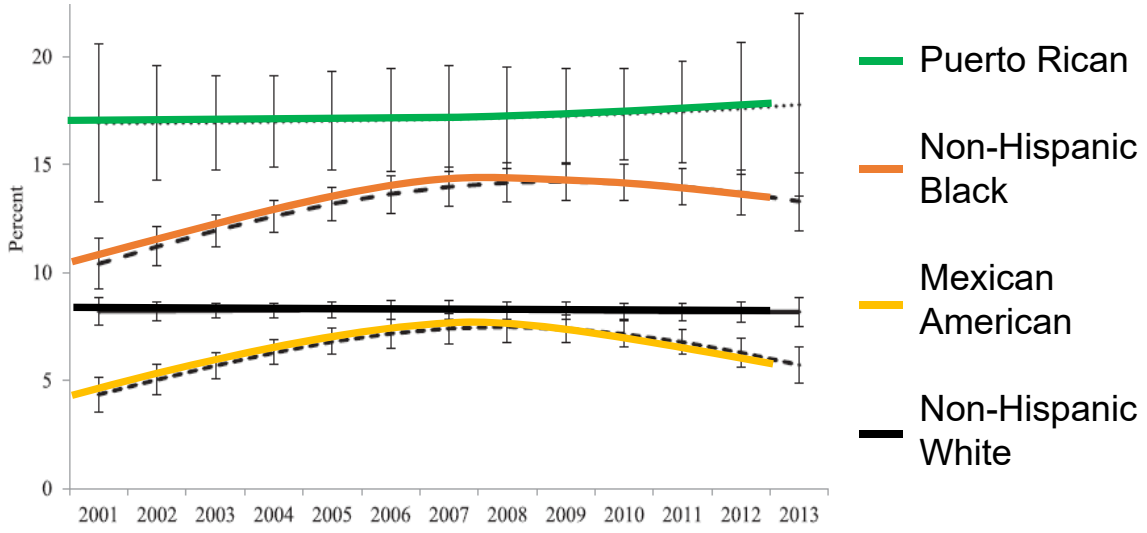
Practice Recommendations

- ICS are best first line maintenance therapy
- LABAS are safe and can be used second line
- Consider novel treatments: SMART, tiotropium
- MDIs are as effective as nebulizers
- Consider 2 days of dexamethasone for AEA

The Burden

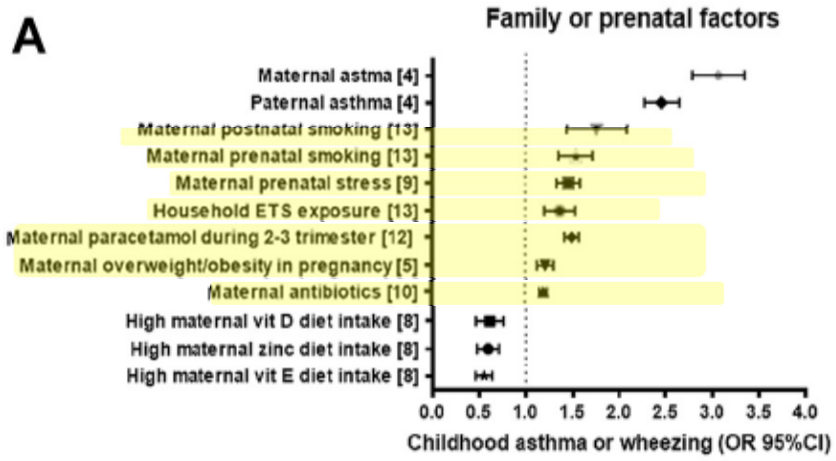


The Burden

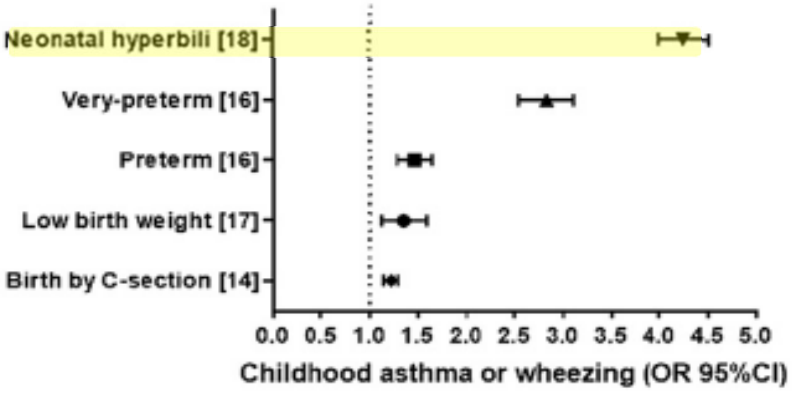


Reducing the Burden

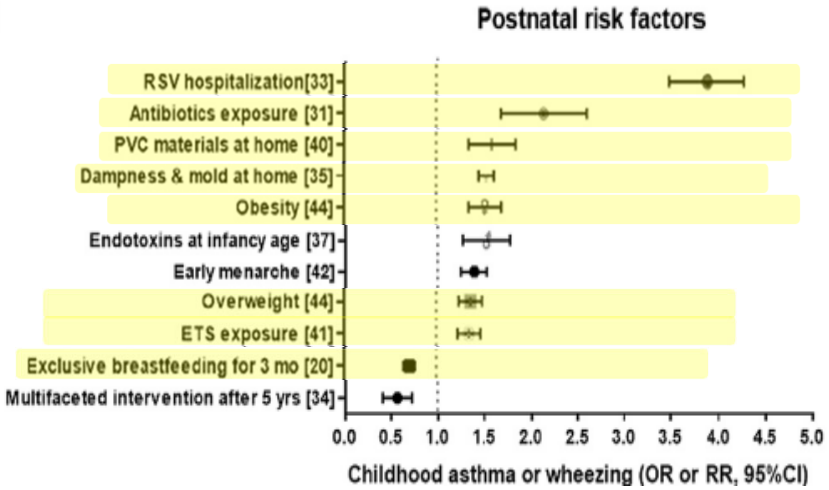
Prenatal



Perinatal

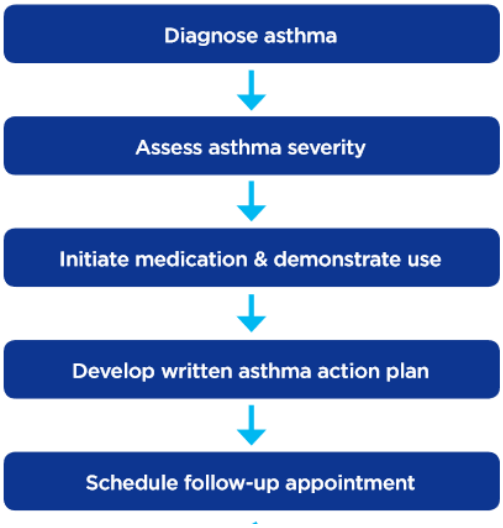


Postnatal

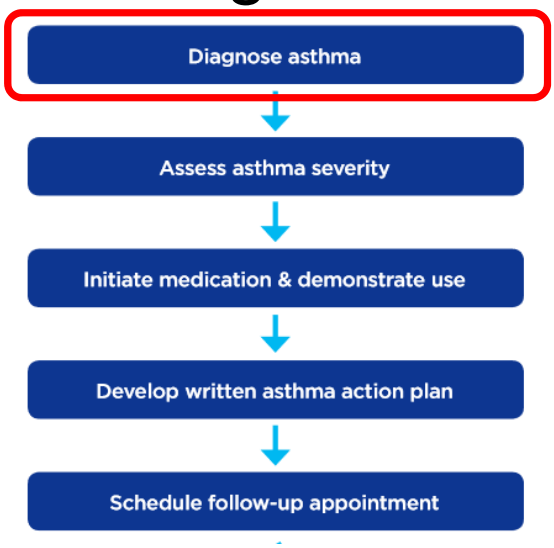


Current Guideline Review

Initial Evaluation of Asthma



Diagnosis



Poll Question 1

A 6-year old male presents with frequent episodes of wheezing. His mother reports that he has been having coughing spells at night every 2-3 weeks and will have wheezing approximately 2-3 times a week.

Which of the following is diagnostic of asthma:

A. 3 episodes of wheezing per year and allergic rhinitis
B. Reversibility of at least 12% in baseline FEV1
C. Reversibility of at least 5% in baseline FEV1
D. Non-reversible obstruction of at least 20% FEV1

Asthma Diagnosis

- Reversibility: FEV1 increases by > 200ml and 12% in baseline or 12% predicted FEV1
- Methacholine challenge most sensitive test
- Positive: decrease in FEV1 > 20% at 8 mg/ml
- Decreased FEV1/FVC suggestive of disease
- Normal spirometry does not exclude asthma!

Asthma Predictive Index

Children < 3 years of age with 3 or more episodes of wheezing in a year AND

- 1 Major Criteria
  - Eczema
  - Evidence of allergen sensitivity
  - Parent with asthma

OR

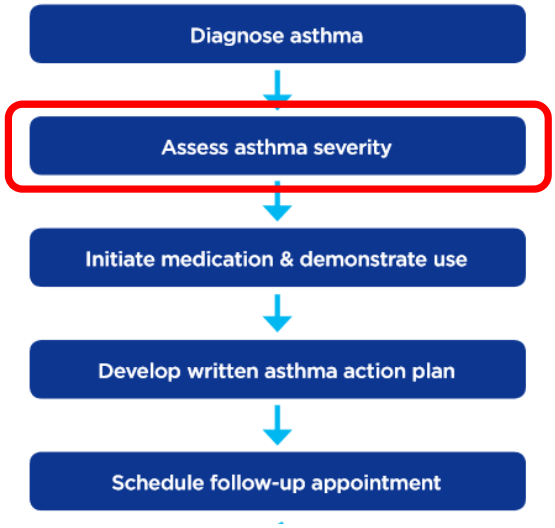
2 Minor Criteria
- Evidence of food allergies
- Eosinophilia >4%
- Wheezing apart from colds

+ Test=76% of children diagnosed with asthma at age 6

Got Asthma? (Really?!)

- Patients (N = 701) underwent spirometry and symptom monitoring
- Patients without asthma per spirometry underwent medication weaning over 4 visits
- Repeat testing ruled out asthma in 203 (33%)
- After 1 year, 6 (2.9%) resumed treatment
- 12 with serious alternative diagnoses

Assessing Severity



Poll Question 2

A 6-year old asthmatic male presents with frequent episodes of wheezing. His mother reports that he has been having coughing spells at night every 2-3 weeks and will have wheezing approximately 2-3 times a week.

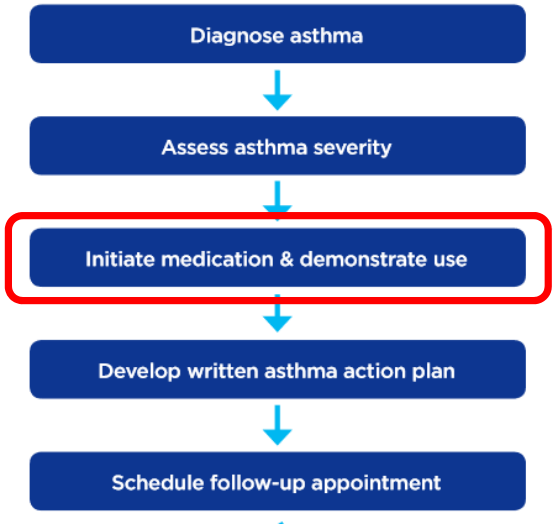
How is the severity of this patient's asthma characterized?

A. Intermittent
B. Mild persistent
C. Moderate persistent
D. Severe persistent

Components of Severity		Intermittent			Mild		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day	
	Interference with normal activity	None			Minor limitation		
	Lung function		Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations			
	➔ FEV_1* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%
	➔ FEV_1/FVC*		>85%	Normal†		>80%	Normal†

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once 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	Normal FEV_1 between exacerbations									
	➔ FEV_1* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	➔ FEV_1/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	*Generally, more frequent and intense events indicate greater severity.*							
						≥2/year	*Generally, more frequent and intense events indicate greater severity.*						
		*Consider severity and interval since last asthma 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.**											

Initiate Medications



Poll Question 3

A 6-year old asthmatic male presents with frequent episodes of wheezing. His mother reports that he has been having coughing spells at night every 2-3 weeks and will have wheezing approximately 2-3 times a week.

Which of the following is first line therapy for control medication for this patient?

A. Long-acting beta agonist (LABA)
B. Leukotriene receptor antagonist (LTRA)
C. Inhaled corticosteroid (ICS)
D. Theophylline

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
	At each step: Patient education, environmental control, and management of comorbidities						
0–4 years of age		Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	medium-dose ICS*	medium-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast + oral corticosteroids
	Alternative Treatment†,‡		cromolyn or montelukast				
	If clear benefit is not observed in 4–6 weeks, and medication technique and adherence are satisfactory, consider adjusting therapy or alternate diagnoses.						
5–11 years of age		Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline[b] OR medium-dose ICS	medium-dose ICS* + LABA*	high-dose ICS* + LABA*	high-dose ICS* + LABA* + oral corticosteroids
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline[§]		medium-dose ICS* + either LTRA* or theophylline[§]	high-dose ICS* + either LTRA* or theophylline[§]	high-dose ICS* + either LTRA* or theophylline[§] + oral corticosteroids
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
≥12 years of age		Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* OR medium-dose ICS*	medium-dose ICS* + LABA*	high-dose ICS* + LABA* AND consider omalizumab for patients who have allergies**	high-dose ICS* + LABA* + oral corticosteroid[§§] AND consider omalizumab for patients who have allergies**
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline[§]	low-dose ICS* + either LTRA,* theophylline,[§] or zileuton[‡‡]	medium-dose ICS* + either LTRA,* theophylline,[§] or zileuton[‡‡]		
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				

		STEP 1	STEP 2	STEP 3	STEP 4
5–11 years of age		Intermittent Asthma	Persistent Asthma: Daily Me Consult with asthma specialist if step 4 care or higher is req		
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline[b] OR medium-dose ICS	medium-dose ICS* + LABA*
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline[§]		medium-dose ICS* + either LTRA* or theophylline[§]
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**		

Box 3-5B
Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

REVIEW RESPONSE
ASSESS
ADJUST

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, or medium dose ICS	Medium dose ICS-LABA Refer for expert advice	Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE
Other controller options	*Low dose ICS taken whenever SABA taken*; or daily low dose ICS*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken**	*Low dose ICS+LTRA*	*High dose ICS-LABA, or add-on tiotropium, or add-on LTRA*	*Add-on anti-IL5, or add-on low dose OCS, but consider side-effects*
RELIEVER	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; separate ICS and SABA inhalers; only one study in children

Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

REVIEW RESPONSE
ASSESS
ADJUST

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ICS for Everyone?

- 2016 industry-funded RCT (N=7100, ages 4-66) mild asthma
  - Randomized to budesonide or placebo daily x 3 years
  - ICS group with 50% fewer severe asthma-related events vs placebo regardless of symptom frequency at baseline
  - ICS group with 8 fewer adverse events per 1000 patient-years
  - Absolute difference: small; could consider ICS in patients with infrequent symptoms (2 days/week or less)
- NHLBI/NAEPP guidelines still rec ICS only for patients with symptoms on 3 or more days/week

Adult Height and ICS

- 2012 RCT: 1000 children ages 5-13
  - Treated with ICS, nedocromil or placebo for 4 yrs
  - Height measured in adulthood (mean age 25)
  - ICS caused modest height reduction of 1.2 cm
  - Most pronounced in girls
- 2014 Cochrane Review
  - 0.48 cm/yr in growth velocity
  - 0.61 cm change in baseline height at 1yr

What About Other Therapies?

5–11 years of age	STEP 1	STEP 2	STEP 3	STEP 4
	Intermittent Asthma	Persistent Asthma: Daily Me Consult with asthma specialist if step 4 care or higher is req		
Preferred Treatment[†]	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline[(b)]	medium-dose ICS* + LABA*
Alternative Treatment[†,‡]		cromolyn, LTRA,* or theophylline[§]	OR medium-dose ICS	medium-dose ICS* + either LTRA* or theophylline[§]
		Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**		

Cromolyn and Theophylline

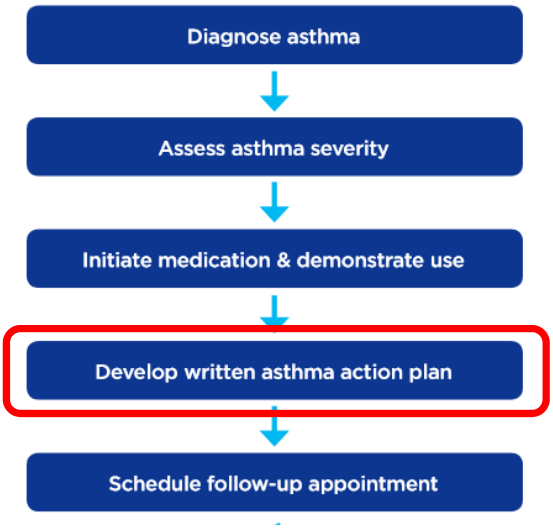
- 2011 Cochrane Review (23 studies, N=1026) evaluated efficacy of cromolyn
  - Cromolyn no better than placebo in symptom free days
  - Small decrease in bronchodilator use
- 2009 Cochrane Review (36 studies, N=2838) evaluated efficacy of theophylline
  - Theophylline better than placebo
  - ICS better than theophylline alone in alleviating symptoms

LTRAs

- Leukotriene receptor antagonists (LTRA) single agent for control in mild persistent

- 2012 Cochrane Review (19 studies, N=3333) examining LTRA vs. ICS
  - Increase in exacerbations (NNH=28)
  - Increase in hospitalizations
  - Increase need for rescue treatments
  - Decreased quality of life
  - Increase in nighttime symptoms

Develop Asthma Action Plan



Asthma Action Plan

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number _____ Hospital/Emergency Department Phone Number _____

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____
(80 percent or more of my best peak flow)

My best peak flow is: _____

Take these long-term control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
Before exercise ❒ _____	❒ 2 or ❒ 4 puffs _____	5 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____
(50 to 79 percent of my best peak flow)

First — **Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.**

_____ (short-acting $beta_2$-agonist) ❒ 2 or ❒ 4 puffs, every 20 minutes for up to 1 hour
❒ Nebulizer, once

Second — **If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:**
❒ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:
❒ Take: _____ (short-acting $beta_2$-agonist) ❒ 2 or ❒ 4 puffs or ❒ Nebulizer
❒ Add: _____ (oral steroid) mg per day For _____(3–10) days
❒ Call the doctor ❒ before/ ❒ within _____ hours after taking the oral steroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____
(50 percent of my best peak flow)

Take this medicine:

❒ _____ (short-acting $beta_2$-agonist) ❒ 4 or ❒ 6 puffs or ❒ Nebulizer
❒ _____ (oral steroid) mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:
- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS
- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ❒ 4 or ❒ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance** _____ (phone) **NOW!**

See the reverse side for things you can do to avoid your asthma triggers.

Asthma Action Plans (AAP)

- 2017 CR of 15 RCTs, N=3062 (AAP vs no AAP: N=2602; AAP plus education vs education alone: N=460)
- Ages 22-49, most studies 6 months long
- No benefit or harm with AAPs on ED visits or admissions (OR 0.75; 95% CI, 0.45-1.24; N=1385)
- No benefit or harm with AAP + education on ED visits or hospitalizations (OR 1.1; 95% CI, 0.27-4.32; N=70)
- Similar results with AAP on steroids, symptoms, function
- Overall evidence rated “low/very low”

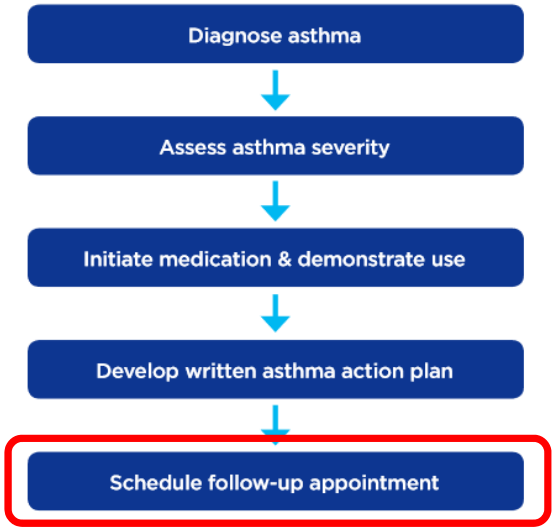
Asthma Action Plans (AAP)

- 2006 Cochrane: 3 RCTs, (N=355), children, symptom-based vs. peak-flow AAP
  - Less acute visits with symptom-based AAP
  - Children preferred symptom vs. peak flow
  - No difference in need of oral steroids, admissions, quality of life

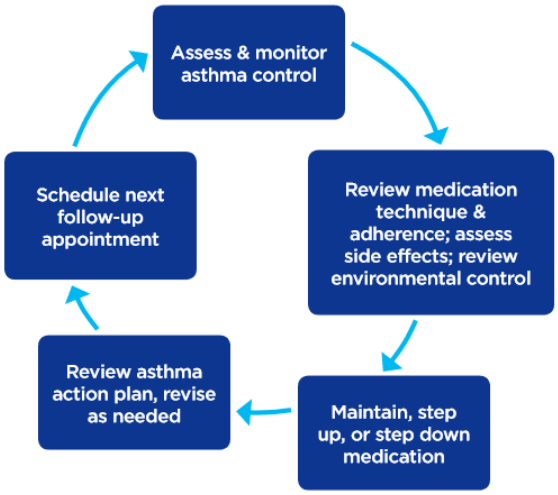
AAPs and Steroids

- 2012 RCT (N=230, 5-12 years), Australia
  - Oral prednisolone 1mg/kg vs. placebo
  - May reduce symptoms and healthcare use
  - May be useful with experienced parents
  - Not recommended for preschool children
- 2016 Cochrane (3 RCTs, N=422)
  - Increasing ICS does NOT help reduce ER visits, oral steroids, hospitalizations
- Two 2018 RCT's quadruple-dose ICS for symptoms
  - Completely ineffective in children; minimal benefit in adults

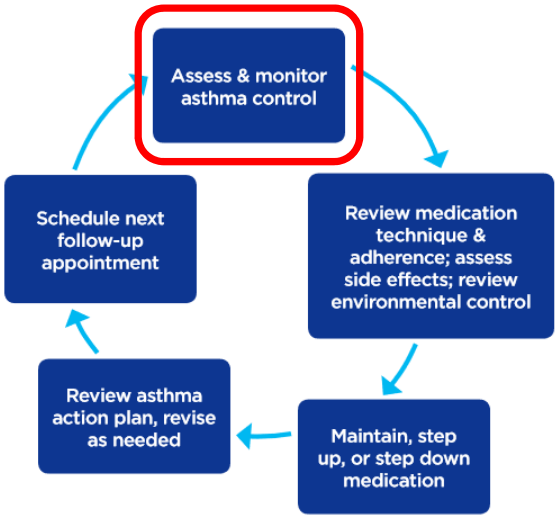
Follow-Up



Follow-up Visits



Assess Control



asthma.com

Patient's Name: _____

Today's Date: _____

Childhood Asthma Control Test for children 4 to 11 years

Know your score.

Parent or Guardian: The Childhood Asthma Control Test* is a way to help your child's healthcare provider determine if your child's asthma symptoms are well controlled. Take this test with your child (ages 4 to 11). Share the results with your child's healthcare provider.

Step 1: Have your child answer **the first four questions (1 to 4).** If your child needs help, you may help, but let your child choose the answer.

Step 2: Answer the last **three questions (5 to 7)** on your own. Don't let your child's answers influence yours. There are no right or wrong answers.

Step 3: Write the number of each answer in the score box to the right.

Step 4: Add up each score box for the total.

Step 5: Take the COMPLETED test to your child's healthcare provider to talk about your child's total score.

19 or less

IF YOUR CHILD'S SCORE IS 19 OR LESS, **Your child's asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your child's healthcare provider to talk about your child's results.**

NOTE: If your child's score is 12 or less, his or her asthma may be very poorly controlled. Please contact your child's healthcare provider right away.

Have your child complete these questions.

1. How is your asthma today?

0	1	2	3
Very bad	Bad	Good	Very good

2. How much of a problem is your asthma when you run, exercise or play sports?

0	1	2	3
It's a big problem, I can't do what I want to do.	It's a problem and I don't like it.	It's a little problem but it's okay.	It's not a problem.

3. Do you cough because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.

4. Do you wake up during the night because of your asthma?

0	1	2	3
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5	4	3	2	1	0
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5	4	3	2	1	0
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday

7. During the last 4 weeks, how many days did your child wake up during the night because of the asthma?

5	4	3	2	1	0
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday

SCORE

TOTAL

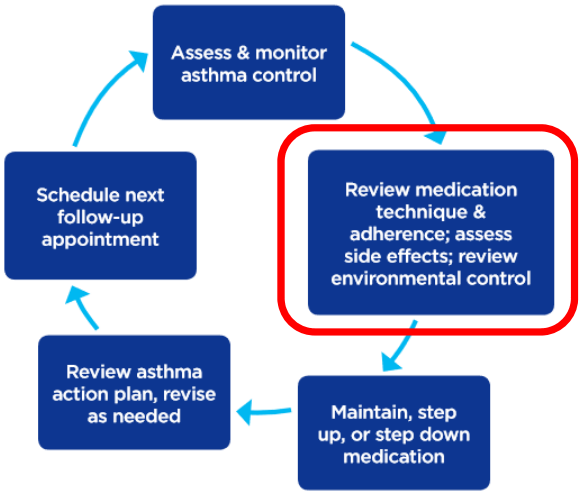
*The Childhood Asthma Control Test was developed by GSK.

This material was developed by GSK.

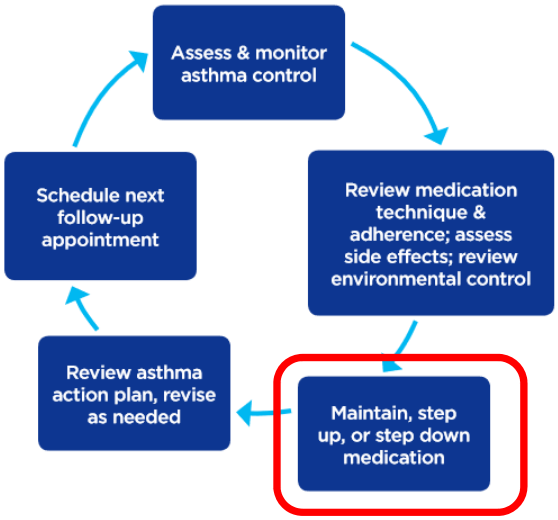
					SCORE
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?					
All of the time **[1]**	Most of the time **[2]**	Some of the time **[3]**	A little of the time **[4]**	None of the time **[5]**	.....
2. During the past 4 weeks, how often have you had shortness of breath?					
More than Once a day **[1]**	Once a day **[2]**	3 to 6 times a week **[3]**	Once or twice a week **[4]**	Not at all **[5]**	.....
3. During 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 **[1]**	2 to 3 nights a week **[2]**	Once a week **[3]**	Once or twice **[4]**	Not at all **[5]**	.....
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?					
3 or more times per day **[1]**	1 to 2 times per day **[2]**	2 or 3 times per week **[3]**	Once a week or less **[4]**	Not at all **[5]**	.....
5. How would you rate your asthma control during the past 4 weeks?					
Not Controlled at All **[1]**	Poorly Controlled **[2]**	Somewhat Controlled **[3]**	Well Controlled **[4]**	Completely Controlled **[5]**	.....

TOTAL: .....

Review Inhaler Technique



Adjust Medications



Poll Question 4

A 6-year old asthmatic male presents with frequent episodes of wheezing, despite ICS. His mother reports that his nighttime symptoms occur once a month but he continues to have wheezing approximately 2 times a week.

Which of the following is the best option for stepping up control therapy?

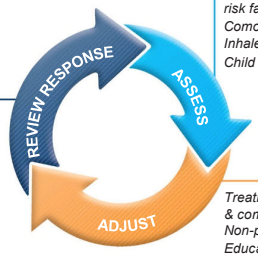
A. Adding tiotropium
B. Switching to montelukast
C. Adding theophylline
D. Adding LABA

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
		At each step: Patient education, environmental control, and management of comorbidities					
0–4 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 3 care or higher is required. Consider consultation at step 2.				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	medium-dose ICS*	medium-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast	high-dose ICS* + either LABA* or montelukast + oral corticosteroids
	Alternative Treatment†,‡		cromolyn or montelukast				
		If clear benefit is not observed in 4–6 weeks, and medication technique and adherence consider adjusting therapy or alternate diagnoses.					
5-11 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 4 care or higher is required				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + either LABA,* LTRA,* or theophylline[b] OR medium-dose ICS	medium-dose ICS* + LABA*		
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline[b]		medium-dose ICS* + either LTRA* or theophylline[b]		
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				
≥12 years of age		**Intermittent Asthma**	**Persistent Asthma: Daily Medication** Consult with asthma specialist if step 4 care or higher is required				
	Preferred Treatment†	SABA* as needed	low-dose ICS*	low-dose ICS* + LABA* OR medium-dose ICS*	medium-dose ICS* + LABA*	LABA* AND consider omalizumab for patients who have allergies**	LABA* + oral corticosteroid[gg] AND consider omalizumab for patients who have allergies**
	Alternative Treatment†,‡		cromolyn, LTRA,* or theophylline[b]	low-dose ICS* + either LTRA,* theophylline,[b] or zileuton[ii]	medium-dose ICS* + either LTRA,* theophylline,[b] or zileuton[ii]		
			Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**				

low-dose ICS* + either LABA,* LTRA,* or theophylline[b] OR medium-dose ICS

Box 3-5B
Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, or medium dose ICS	Medium dose ICS-LABA Refer for expert advice	Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE
Other controller options	*Low dose ICS taken whenever SABA taken*; or daily low dose ICS*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken**	*Low dose ICS+LTRA*	*High dose ICS-LABA, or add-on tiotropium, or add-on LTRA*	*Add-on anti-IL5, or add-on low dose OCS, but consider side-effects*
RELIEVER	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; separate ICS and SABA inhalers; only one study in children

Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

REVIEW RESPONSE
ASSESS
ADJUST

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

Risks of LABA's

- Cochrane Reviews of LABA safety
  - 6 deaths in combo formoterol vs. 1 in ICS alone
  - No difference in non-fatal events
  - Salmeterol deaths all occurred with drug alone
  - No diff in head to head comparisons
- 2010 FDA black box warning placed on LABA's
- FDA mandated surveillance studies…
- FDA dropped black box warning on ICS/LABA in Dec 2017 (still NEVER use LABA alone in asthma)

The Return of the LABAs

- 2016 RCT (N=11,693): formoterol + budesonide (Symbicort) vs budesonide alone in patients > 12 yrs
  - Combo reduced exacerbations 16.5% (HR 0.84; 95% CI, 0.74-0.94)
  - No diff in asthma-related side effects (43 vs 40); 2 deaths in combo
- 2016 RCT (N=6028): salmeterol + fluticasone (Advair) vs. fluticasone alone in children 4-11
  - Combo non-inferior to fluticasone alone; no diff in serious asthma related side effects (21 vs. 27); no deaths in either group
  - No benefit to add on LABA, but safety was primary endpoint

LABAS Are Safe!

- 2018 meta-analysis (4 RCTs, N=36,010)
  - Compared safety of ICS alone vs. ICS/LABA
  - No difference in intubations, death at 26 wks
  - No difference in hospitalizations
  - Decreased exacerbations in ICS/LABA (9.8% vs. 11.7%)

ICS plus LABA…Right Away?

- 2013 Cochrane Review, 27 trials, N=8050
- RCT's comparing ICS + LABA with ICS alone
- Combo ICS/LABA no better than ICS alone
- Higher dose ICS superior to add on LABA
- Children responded similarly to adults
- No difference in adverse events

Single Inhaler Therapy (SiT)

- Combo formoterol/budesonide (SiT)
- 2013 Cochrane Review: 13 studies of over 13,352 patients; no children < 12; all industry funded
- Key results:
  - Asthma exacerbations requiring oral steroids
  - ER visits and hospitalizations
  - Adverse events/discontinuation higher in SiT group
  - NNT 100 to prevent admission or ER visit

Most Recent SiT Evidence

- SYGMA 1 and SYGMA 2 trials NEJM 2018
  - Non-inferior for severe exacerbations vs ICS + SABA
  - 64% reduction in severe exacerbations vs SABA alone
  - Greater symptom reduction, better adherance
- 2019 Lancet: 885 New Zealanders, mild asthma
  - 30% fewer severe exacerbations, 50% less steroid
- SiT limitations:
  - Off label, not FDA approved
  - Only ages 12+ studied
  - Only budesonide/formoterol Turbohaler studied (not in US)

LTRA as Adjunct

- 2011 pragmatic trial (N=352 adults and children)
  - LTRA equivalent at 2 months to ICS+LABA
  - Non-equivalent at 2 years
- 2010 trial (N=182 children) compared adjuncts:
  - Increased ICS dose
  - Added LABA
  - Added LTRA
  - Overall best response on ACT with added LABA

Tiotropium for Asthma

- 2012 industry funded RCT (N=900)
  - All with asthma not controlled on LABA or ICS
  - DOE improvements of pulmonary function
  - 1 less exacerbation after 8 yrs of treatment!
- Multiple Cochrane Reviews in 2015/2014
  - LAMA add on therapy improves lung function
  - Reduces exacerbations compared to ICS alone
  - No difference in exacerbations vs ICS/LABA
- FDA approved ages 6+

Biologics: “The Mab’s”

- Omalizumab, benralizumab, mepolizumab, dupilumab
- Anti-IgE, anti-IL 5, anti-IL 4/13
- “Mab’s”:
  - Reduce asthma exacerbations
  - Reduce hospitalizations
  - Generally well-tolerated
  - Reduce/withdraw steroids
- Step 5 medications, rx with pulmonary/allergy consultation
- Expensive! One vial omalizumab: $826! dupilumab: $3K/month!
- Risks: anaphylaxis (esp omalizumab), shingles (mepolizumab)

Acute Asthma Management

Poll Question 5

In a 6-y.o. presenting with an asthma exacerbation, which of the following is the best initial action?

A. Administer albuterol via MDI
B. Start albuterol nebulizer
C. Administer IV albuterol
D. Administer ICS

Albuterol

- 2009 Cochrane review:
  - MDIs as effective as nebulizers
  - MDIs may reduce hospital length of stay compared to nebulizers
- 2003 RCT (N=168) children 2-24 months:
  - Less admissions with MDI vs. nebulizer

Albuterol/Ipratropium

- 2016 Systematic review (N=2497):

  In children under 3 years with an exacerbation
  - 44% reduction in admissions with MDI vs. neb (NNT=10)
  - Ipratropium did not appear to help (but evidence is poor)

  In children 3-18 years, and adults
  - No likely difference between MDI and nebulizer
  - Ipratropium reduced hospitalizations vs SABA alone
  - Most guidelines rec combo; stop once stable/admitted

Steroids in Exacerbations

- ICS = NO! ORAL = YES!
- ICS in the ER for acute exacerbations
  - 2016 Cochrane: no decrease in admissions
- Choice of oral steroid?
  - Prednisone vs. dexamethasone
  - 2 days of dex as good as 5 days of prednisone
  - Single dose of dex as good as 3 days of prednisone

Novel ICS Use

- Quadruple-dose ICS for worsening symptoms
  - Two 2018 RCT's tested this hypothesis
  - Completely ineffective in children; minimal benefit in adults
  - Use oral/IM steroids for exacerbations
- As-needed ICS without daily maintenance therapy
  - Two 2018 studies with 8000 patients with mild persistent asthma
  - Compared daily ICS to as need budesonide/formoterol inhaler
  - No difference in exacerbations, less ICS exposure, more symptoms
- Single maintenance and reliever therapy ("SMART")
  - Budesonide/formoterol for BOTH maintenance and rescue therapy
  - No albuterol inhaler
  - 2018 meta-analysis: SMART decreased exacerbations, not symptoms

Exercise-Induced Bronchoconstriction

- Formal postexercise spirometry for diagnosis
- SABA 15 min prior to exercise
- Alternant: mast cell stabilizer, anticholinergic
- NO LABA's!
- If use SABA daily: ICS or LRA
- Nondrug: warm up first, use mask or scarf

Influenza Vaccine

- 2013 Cochrane Review of 18 trials
  - No reduction in influenza-related exacerbations
  - No apparent risk from inactivated vaccine
  - No risk from live intranasal influenza vaccination
  - Vaccines do not worsen asthma
- 2017 meta-analysis of 35 studies (142K)
  - Pooled efficacy of 81%
  - Reduced febrile illness by 72%
  - Reduced exacerbations by 59-78%

Asthma and Supplements

- Vitamin D MAY prevent exacerbations
  - 2018 RCT (N=250): vitamin D vs placebo; no difference in time to 1st exacerbation
  - 2016 Cochrane: 9 trials, 435 children, 658 adults showed reduction in exacerbations (0.44 to 0.28 per person-year), ER visits, and hospitalizations (6% to 3% per year)
- Caffeine improves airways function for up to four hours
  - 7 studies of 75 patients
  - Improved FEV1 by 12-18%
  - May need to avoid caffeine for at least four hours prior to spirometry

Asthma and Supplements

- Probiotics during pregnancy or early infancy do not prevent asthma
  - Meta-analysis of 20 RCTs included 4866 children
  - Various combinations/doses of probiotics
  - Followed children from 2 to 6 years after birth
  - No evidence of benefit
  - 2017 RCT (N=184 infants) found no reduction at 5 years
- Vitamin C not beneficial in asthma
  - 9 studies, 330 participants
  - One study with drop in FEV1 post-exercise

Asthma and Pregnancy

- Asthma may improve, worsen or stay the same
  - Mild: 12.6% exacerbation/2.3% hospitalization
  - Moderate: 25.7%/6.8%
  - Severe: 51.9%/26.9%
- 15-20% increased risk of complications
  - Mortality, pre-e, preterm delivery, low birth weight
- Monitor peak flows bid +/- spirometry

Smoking cessation!

Asthma and Pregnancy

- Medication safety
  - Albuterol (C), ICS (B/C), LABA (C), LRA (B), Ipratrop (B)
  - Carboprost (avoid!)
- "Best" data: albuterol, budesonide, salmeterol
- Less data: formoterol, LRA's
- No diff in malformations b/t ICS vs. LABA/ICS
- AEA in pregnancy tx'ed the same!!

Nuts and Pregnancy

- Avoiding nuts during pregnancy controversial
- Danish Birth Cohort of 101,045 pregnancies
- Self-report data from validated questionnaire
- Nut intake inversely associated with asthma
- Consumption may decrease risk of allergies
- Nut consumption not harmful

Fish Oil in Pregnancy

- 2016 RCT in Danish women (N = 695): LCPUFA during pregnancy to reduce wheezing disorders in children
- Compared 1g of fish oil to identical olive oil
- Supplementation 22-26 weeks gestation until 1 week after; children followed at least 5 years
- Wheezing disorders lower in fish oil group (16.9% vs 23.7%; HR 0.69; 95% CI 0.49 - 0.97, NNT 15)
- Women with lowest baseline LCPUFA levels benefited most (17.5% vs 34.1%; HR 0.46; 0.25 - 0.83, NNT 5.6)
- No reduction in exacerbations, allergic sensitization, or eczema

Practice Recommendations

- ICS are best first line maintenance therapy
- LABAS are safe and can be used second line
- Consider novel treatments: SMART, tiotropium
- MDIs are as effective as nebulizers
- Consider 2 days of dexamethasone for AEA

Questions

FMX