AN UPDATE IN ASTHMA

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Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

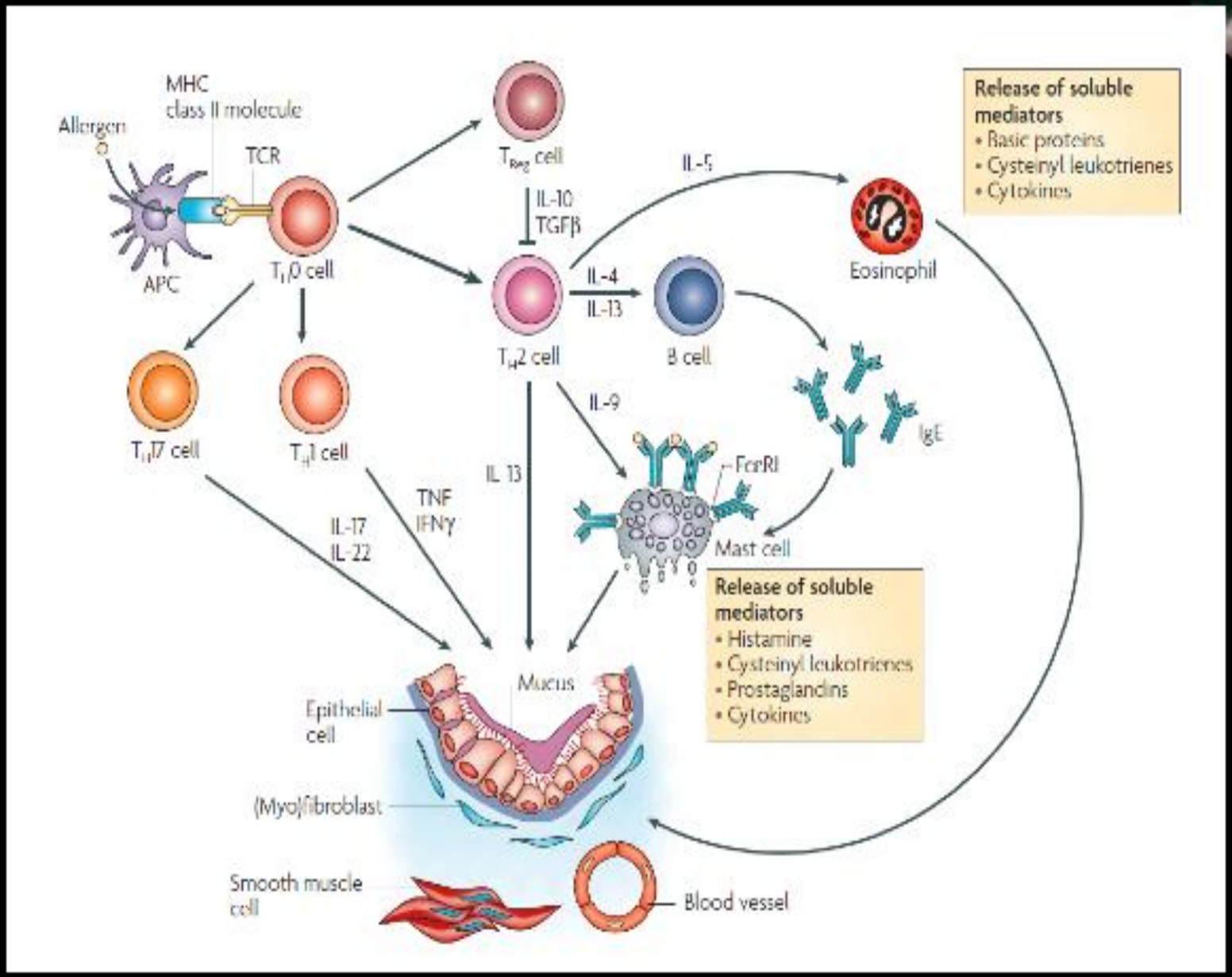
Objectives

- Learn the Asthma Guidelines
- Be able to classify asthma severity
- Be able to determine asthma control
- Be able to successfully treat asthma
- Be able to improve patient outcomes
- Pass your boards

Pathogenesis

- Conventionally considered a T-helper cell type 2 (TH_2)-mediated inflammatory disease
  - Associated with increased interleukin(IL): IL-4, IL-5, and IL-13
    - known to promote inflammation, including tissue eosinophilia and remodeling
- Primarily treated with corticosteroids
- Recognized as a spectrum of diseases with distinct clinical and molecular features encompassing specific disease endotypes

Inflammatory Mechanisms



The Cytokine Players

- Interleukins
  - IL-4 and IL-13
    - Distinct and overlapping roles in asthma
    - Both signal through the type 2 IL-4 receptor and regulated by a master transcription factor, GATA-3
  - IL-4
    - Induces IgE class switching of B cells and vital for TH_2 cell differentiation
  - IL-5
    - Pro-eosinophilic and binds a receptor (IL-5Rα) on eosinophils and basophils that promotes eosinophil recruitment, survival and activation
  - IL-13
    - Promotes cellular influx, **airway hyper-responsiveness**, and **remodeling factors**

Testing

Peak Flow Chart and Device

Sample Peak Flow Chart

Name: *Jane Doe*
My Personal Best Peak Flow Number is *625*
My Green Zone is above *500*
My Yellow Zone is between *312* and *500*
My Red Zone is below *400*

My Controller Medicine: *Advair*
Dose: *250/50 2x per day*
My Fast-Acting Medicine: *Albuterol*
Dose: *2 puffs as needed*

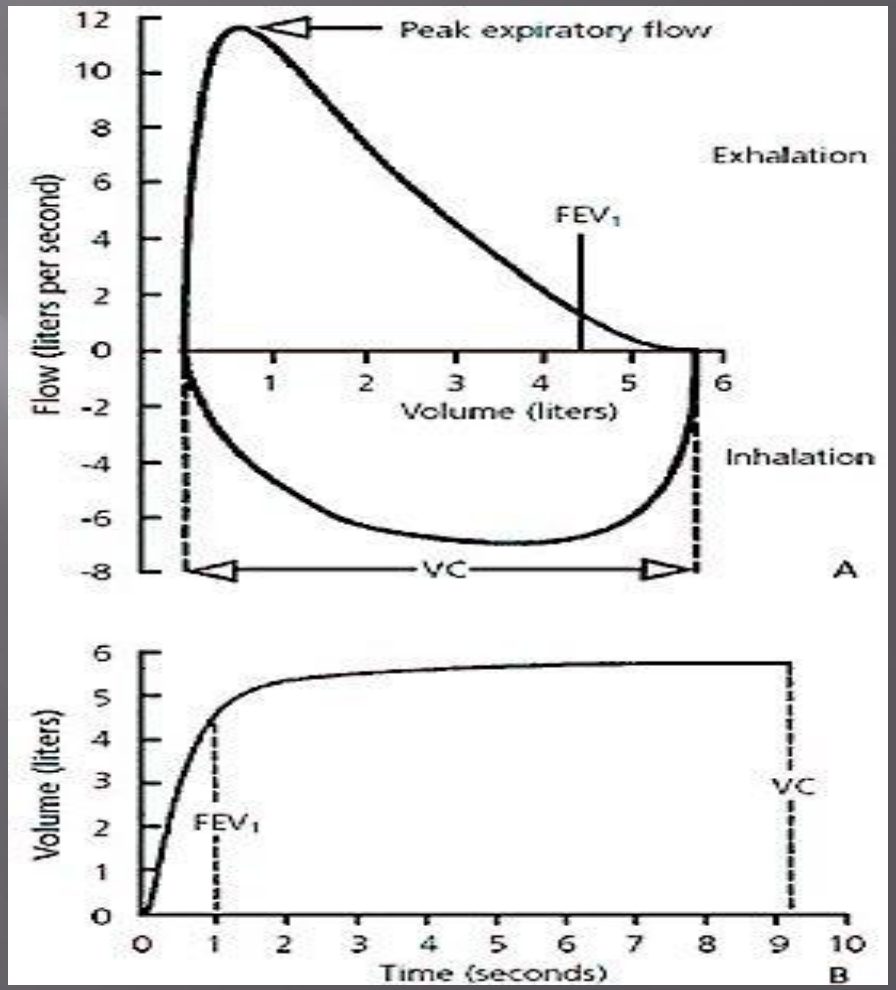
Peak Flow Measurements	Date 1/1	Date 1/2	Date 1/3	Date 1/4	Date 1/5	Date 1/6	Date 1/7	Date 1/8	Date 1/9	Date 1/10	Date 1/11	Date 1/12	Date 1/13	Date 1/14
700														
650														
600	•	•												
550			•						•	•	•			
500				•			•	•				•	•	•
450						•								
400					•									
350														
300														
250														
200														
150														
100														
50														
My Peak Flow Number	*620*	*600*	*550*	*510*	*430*	*480*	*520*	*510*	*560*	*580*	*590*	*500*	*500*	*510*
Asthma Symptoms Experienced					*cough/ wheeze*	*cough/ wheeze*								
Trigger (*i.e.*, pet, exercise, illness, smoke)?					*dog*									
Fast-Acting Medicine Used? (Yes or No)					*yes 2x*	*yes 1x*								

Most peak flow meters come with sample peak flow graphs. It is a good idea to make copies. If you no longer have a sample, you can make your own, or use the one above.

For use in patients >4 years of age

Pulmonary Function Testing

- Forced Vital Capacity – is the total volume of air expired after a full inspiration
  - FVC
- Forced Expiratory Volume 1 - is the volume of air the patient can expel in one second
  - FEV_1



http://meded.ucsd.edu/isp/1998/asthma/html/naep.html#NAEP

Fractional Exhaled Nitric Oxide (FENO)

- During inflammation, higher-than-normal levels of nitric oxide (NO) are released from epithelial cells of the bronchial wall.

- The concentration of NO in exhaled breath, or fractional exhaled nitric oxide (FeNO), can help identify airway inflammation, and thereby support a diagnosis of asthma when other objective evidence is lacking.

Fractional Exhaled Nitric Oxide (FENO)

CLINICAL GUIDE TO INTERPRETATION OF FeNO VALUES[1-3]

MANAGEMENT OF PATIENTS DIAGNOSED WITH ASTHMA, TREATED WITH ICS OR COMBINATION THERAPY

		LOW	INTERMEDIATE	HIGH
	FeNO value (ppb), patients ≥12 years of age	<25	25-50	>50
	FeNO value (ppb), patients <12 years of age	<20	20-35	>35
		In the case of a >40% increase from previously stable levels, interpret as high FeNO.		
	Consider as significant increase in FeNO	Increase >10 ppb from last measurement		Increase >20% from last measurement
	Consider as response to ICS	Decrease >10 ppb from last measurement		Decrease ≥20% from last measurement
CONSIDERATIONS FOR THERAPY	Symptomatic	• Review symptoms and consider alternate diagnoses	• Possible inadequate ICS treatment 1. Check adherence 2. Check for poor inhaler technique • Consider adding other therapy apart from ICS (eg, LABA) • Consider ICS dose increase	• Inadequate ICS treatment 1. Check adherence 2. Check for poor inhaler technique • Consider ICS dose increase • Risk for exacerbation may be increased, especially if patient is not on an ICS • Consider steroid resistance (rare)
	Asymptomatic	• Implies patient is adherent to treatment • Consider dose reduction, or in case of current low ICS dose, consider ICS withdrawal altogether (repeat FeNO 4 weeks later to confirm this judgement; if it remains low, relapse is unlikely)	• No change in ICS dose if FeNO trend is stable over time • Check adherence • Check for poor inhaler technique	• No change in ICS dose if FeNO trend is stable over time • Check adherence • Check for poor inhaler technique
ALSO CONSIDER	Additional or alternative diagnoses to consider in symptomatic patients *Smoking has been shown to reduce FeNO levels.*	• Anxiety/Hyperventilation • Cardiac disease • COPD • GERD • Noneosinophilic asthma • Rhinosinusitis • Vocal cord dysfunction • Cystic fibrosis • Primary ciliary dyskinesia (FeNO <5 ppb)	• High levels of allergen exposure • Infection as a reason for worsening symptoms	• High levels of allergen exposure • Infection as a reason for worsening symptoms

COPD = chronic obstructive pulmonary disease; FeNO = fractional exhaled nitric oxide; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; LABA = long-acting beta agonist.

Fractional Exhaled Nitric Oxide (FENO)

- Many diseases present with symptoms similar to those seen in asthma. Understanding whether airway inflammation is present can help rule out these conditions and support a diagnosis of asthma.
  - Chronic cough
  - Gastroesophageal reflux disease (GERD)
  - Vocal cord dysfunction
  - Bronchitis
  - Chronic obstructive pulmonary disease (COPD)

- Lack of long term studies
- Lack of consistent reference value

Classification

Defining Asthma Severity and Control

Age Categories

- 0–4 years
- 5–11 years
- 12 years and older

- ***Severity*** **to determine where to start the patients treatment point**

Classifying Asthma *Severity* and Initiating Treatment in Children ≥12 Years of Age

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20 –39 yr 80%** **40 –59 yr 75%** **60 –80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/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% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← 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 **(See figure 4–5 for treatment steps.)**		**Step 1**	**Step 2**	**Step 3** and consider short course of oral systemic corticosteroids	**Step 4 or 5** and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

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Asthma Control Test™ (ACT)

					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 or 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 or 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

If your score is 19 or less, your asthma may not be under control.

Control measure is to be used with each visit

Asthma *Control* Classification
Age ≥12 years old

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	1–3x/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% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		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 **(see figure 4–5 for treatment steps)**		• Maintain current step. • Regular followups every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

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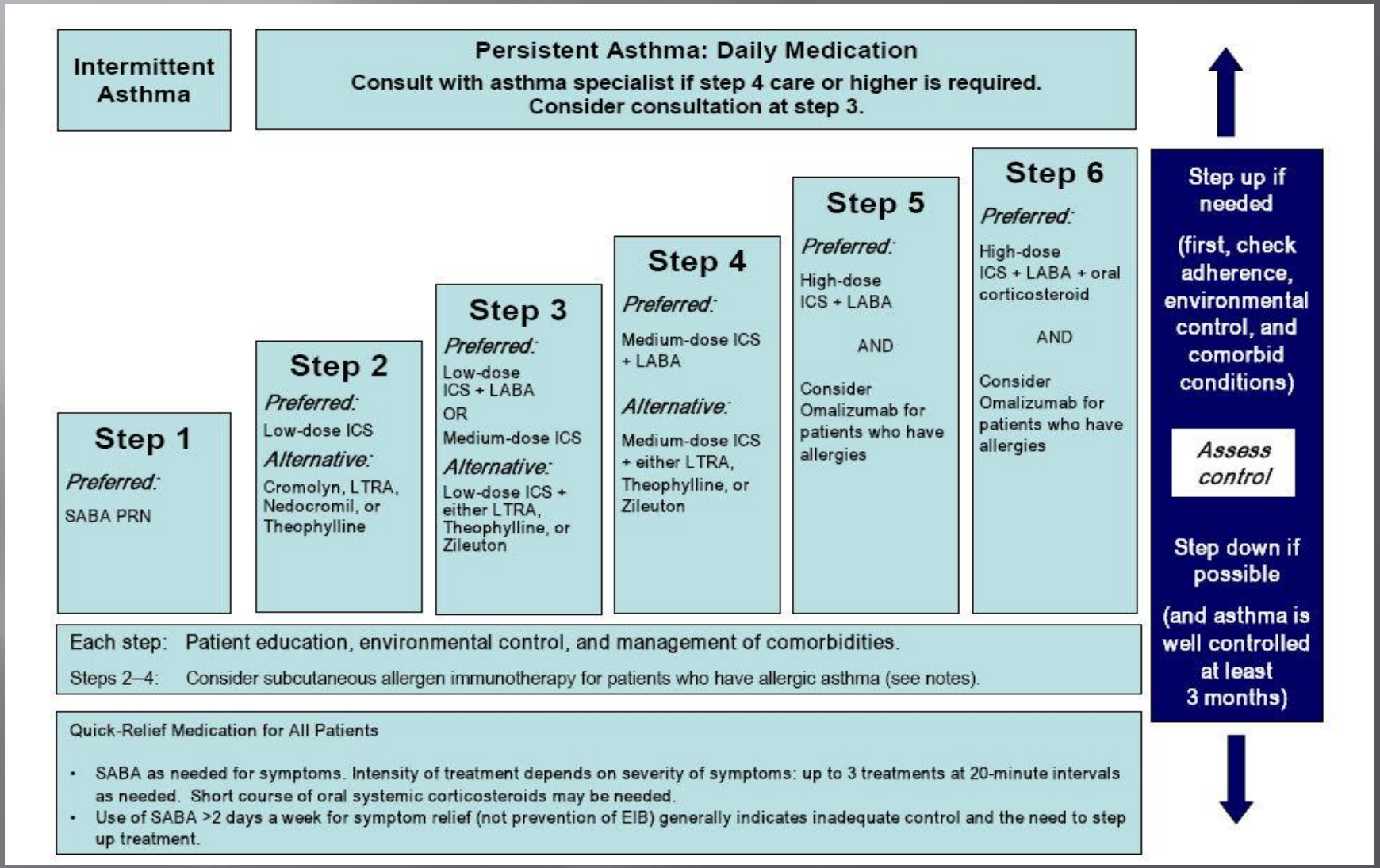
Treatment

Treatment Approach for Patients ≥12 years old



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Practice Cases

Case 1

- 62 year old male with known asthma, comes to your office for a check up.
- He says he has a coughing 'spell' once every week but doesn't have any nighttime symptoms or activity limitations. He used albuterol 2 times since your last visit 4 months ago. His only medication is albuterol and has no history of using any systemic corticosteroids.

- Office pulmonary function testing shows:
  - FEV_1 – 3.8 L (94%)
  - FVC – 4.5 L (89%)
  - FEV_1/FVC – 84 %

Classification of *Severity* in Asthmatic in Patients ≥12 years old

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20 –39 yr 80%** **40 –59 yr 75%** **60 –80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
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Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← 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
				and consider short course of oral systemic corticosteroids	
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Intermittent Controlled Asthma

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
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Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		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 (See figure 4–5 for treatment steps.)		Step 1	Step 2	Step 3	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.		and consider short course of oral systemic corticosteroids	

Asthma Control Classification Age ≥12 years old

	Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year	≥ 2 per year	

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Well Controlled

	Well Controlled	Not Well Controlled	Very Poorly Controlled
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year	≥ 2 per year	

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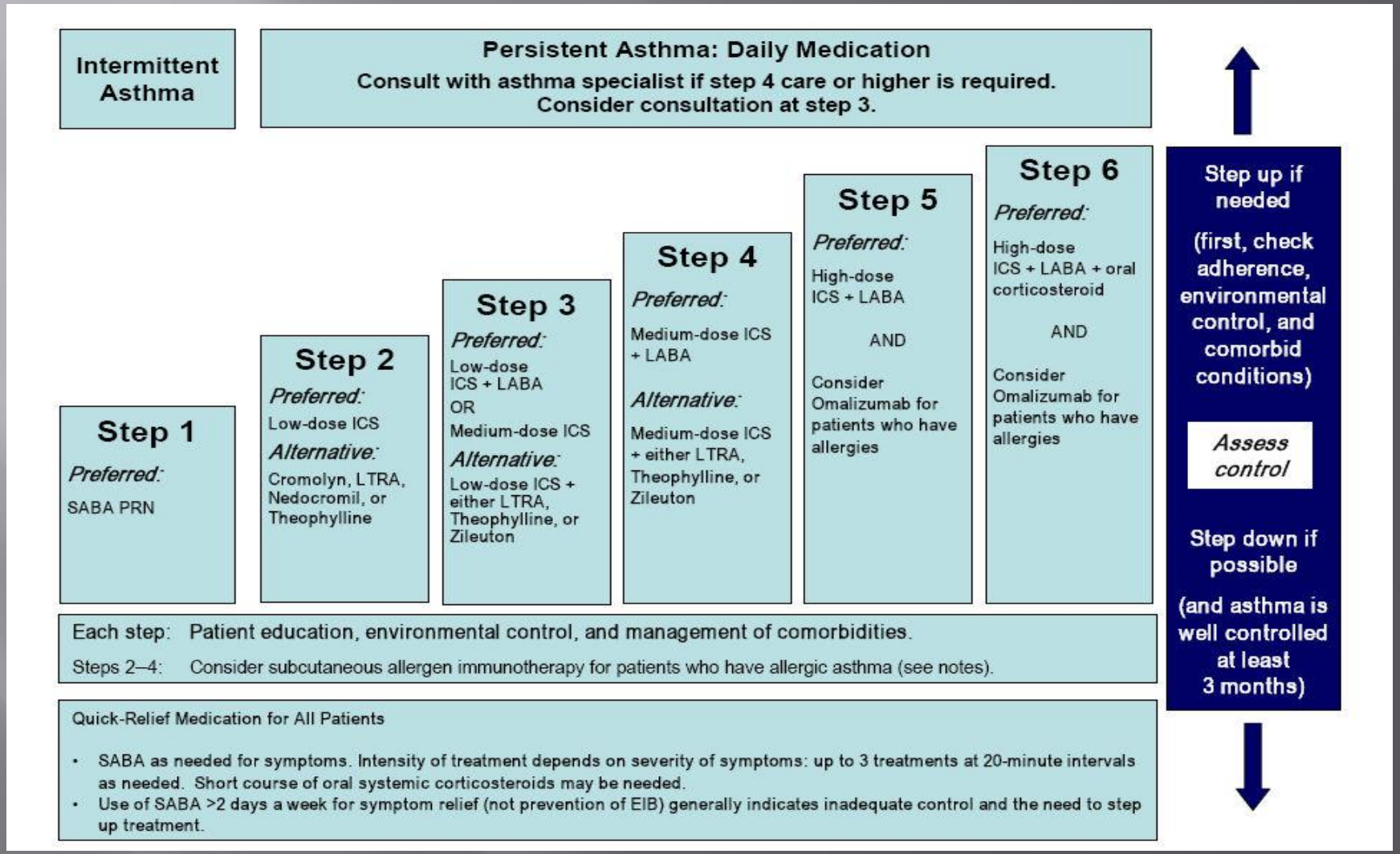
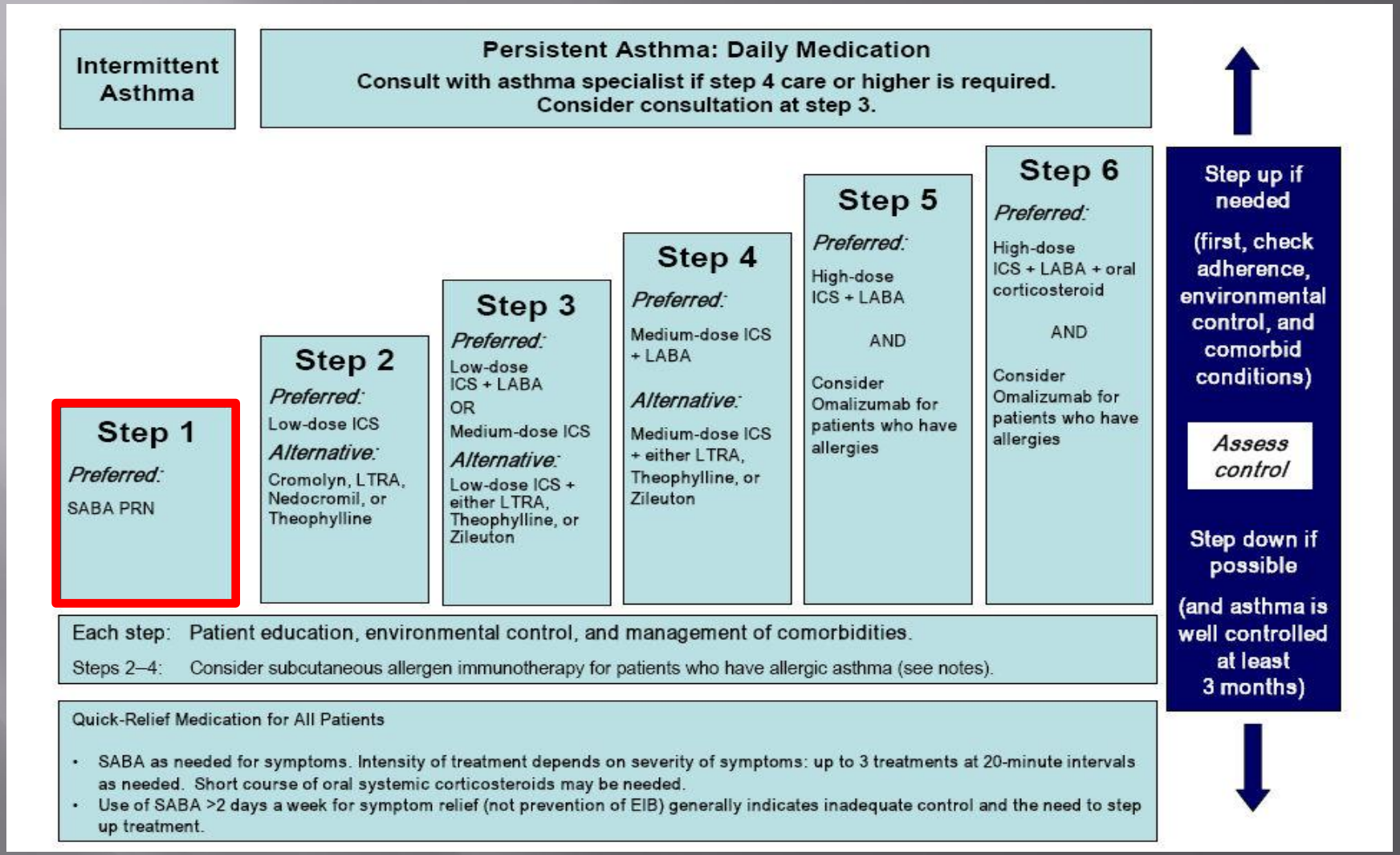
Treatment Approach



Step 1 Therapy



- Plan – continue with SABA PRN and follow up in 6 months for reevaluation

Case 2

- A visibly fatigued 34 year old mom comes into your office with 8 year old boy. She says that she is in a rush today because she needs to get him to soccer.

- Both she and her little boy are suffering from 'hayfever' for the last month all day and night. She says that the last 2 weeks have been terrible and just went to an urgent care and was given a prednisone dose pack.
  - This same thing happened last spring when the trees started to bloom.

- She is actively wheezing on physical examination.

Case 2 Continued

- She is using her albuterol every night because she is coughing so much. She says that the SABA does help her cough. She says that she will also need a refill on her albuterol because she went through the 3 that you gave her already.

- Office pulmonary function testing shows:
  - FEV_1 – 1.6 L (62%)
  - FVC – 3.2 L (65%)
  - FEV_1/FVC – 50 %

- Her current asthma medications are:
  - Budesonide/formoterol fumarate dihydrate 80/4.5mg
  - Albuterol

Classification of *Severity* in Asthmatic in Patients ≥12 years old

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
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	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 normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← 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
				and consider short course of oral systemic corticosteroids	
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Severe Persistent Asthma

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20 –39 yr 80% 40 –59 yr 75% 60 –80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
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Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← 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 (See figure 4–5 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Asthma Control Classification Age ≥12 years old

	Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year	≥ 2 per year	

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Very Poorly Controlled Asthma

	Well Controlled	Not Well Controlled	Very Poorly Controlled
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year		≥ 2 per year

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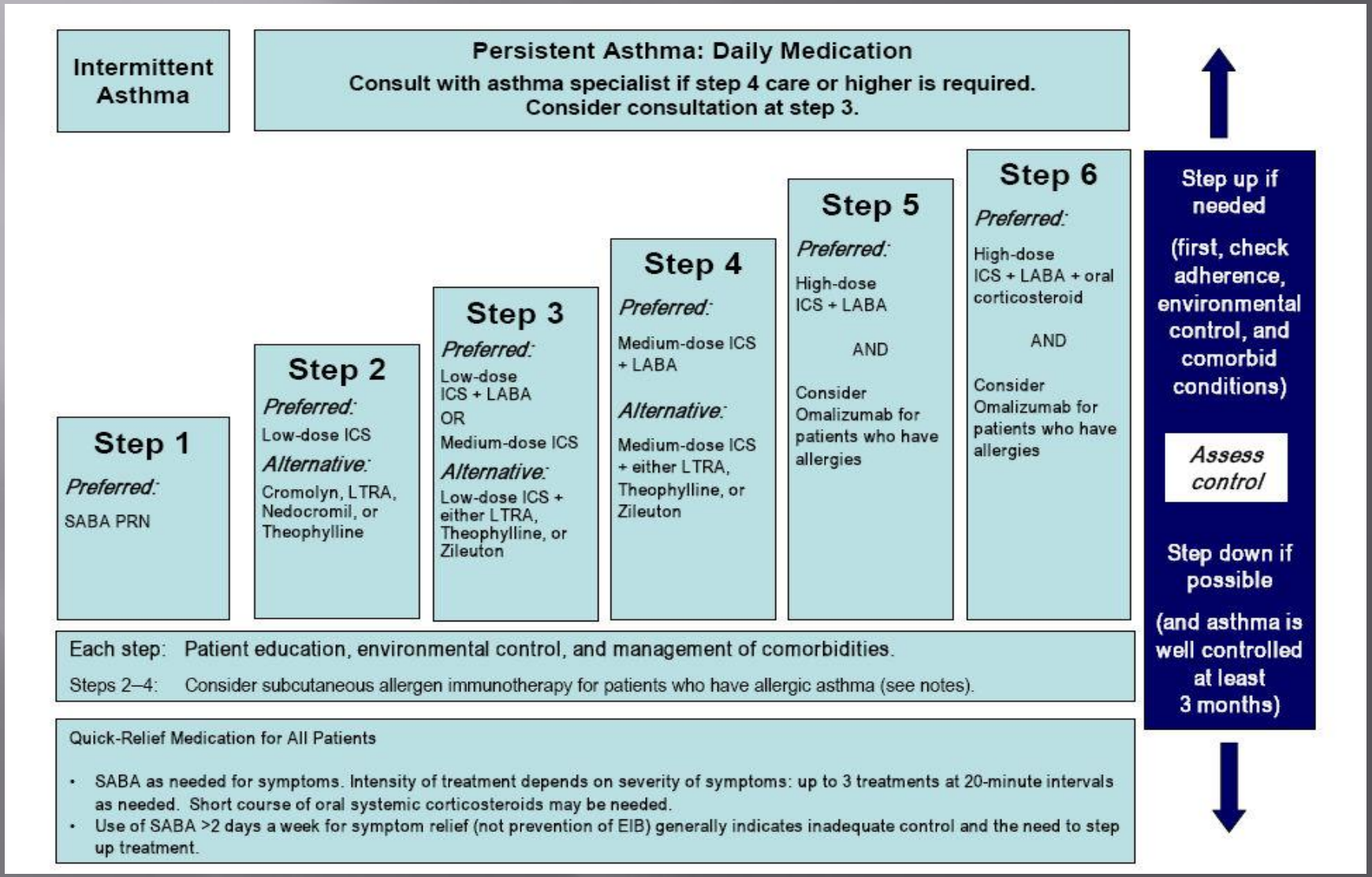
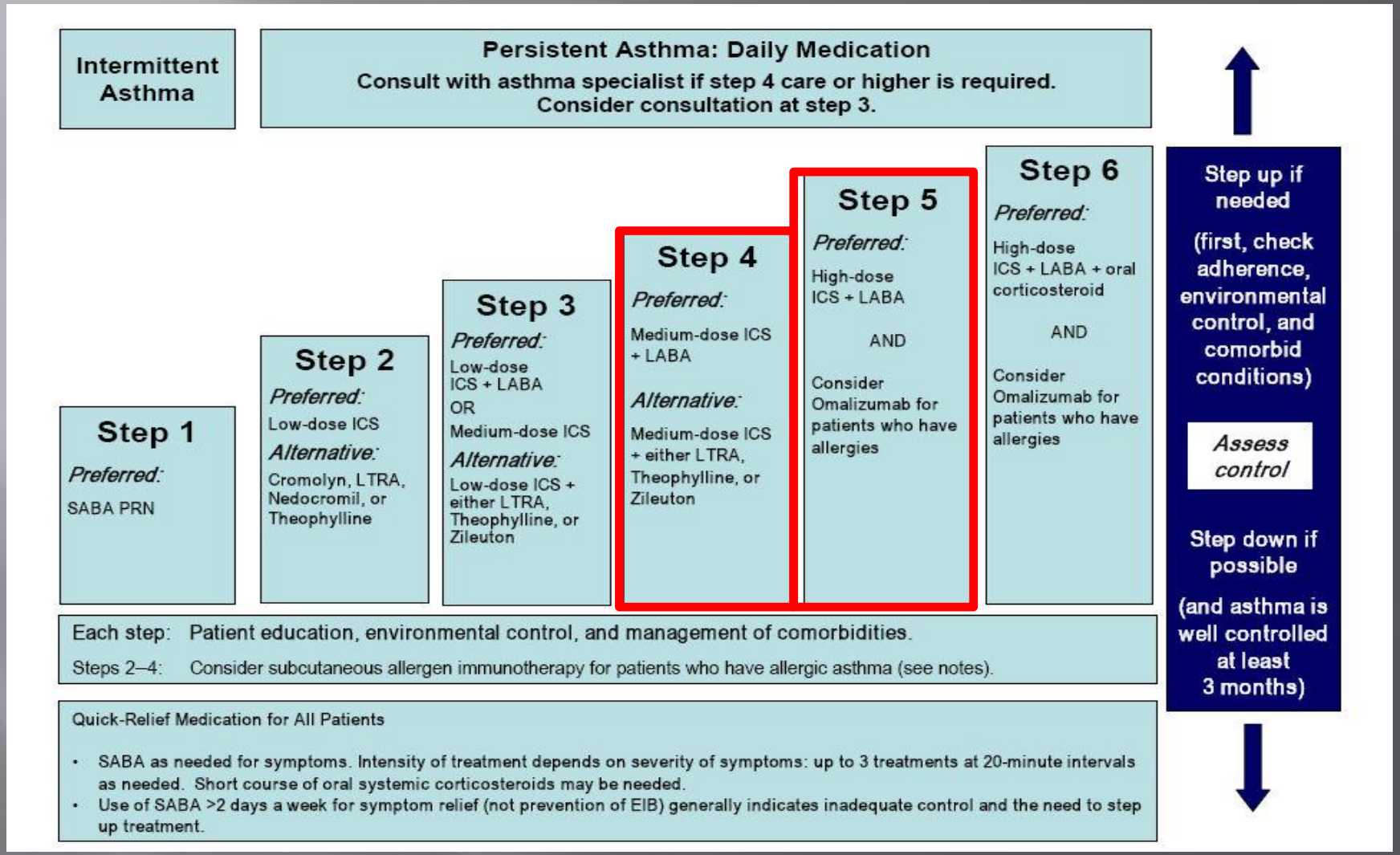
Treatment Approach



Step 4 or 5 Therapy



- Plan – Increase to Medium-dose ICS + LABA and follow up in 3 weeks. Continue SABA PRN

Case 2 Continued

- The patient follows up after 3 weeks and says that she is feeling much better since the frost.

- She no longer has any problems sleeping at night – except when her dog sleeps with her at night. She only uses her albuterol about two times per week. No daily coughing reported but still has 1-2 episodes per week. Increase in her energy is also reported.
  - Office pulmonary function testing shows:
    - FEV_1 – 3.4 L (89%)
    - FVC – 4.5 L (83%)
    - FEV_1/FVC – 76 %

- Plan – ***decrease*** treatment back to 80/4.5mg
  - Continually assess the patients and decrease therapy
  - Assess her atopic status as the possible underlying trigger for her asthma

Case 3

- 26 year old female comes into your clinic with complaint of cough and shortness of breath occurring about once a day every week with some activity limitation. She has noticed over the course of the year that she wakes up 3-4 times a month with similar symptoms. She borrowed her roommate's albuterol and after 6 puffs she feels better. Her roommate is getting angry at her because she is using it every morning before she goes to work.
- Office pulmonary function testing shows:
  - FEV_1 – 3.0 L (72%)
  - FVC – 3.9 L (89%)
  - FEV_1/FVC – 76 %

Classification of *Severity* in Asthmatic in Patients ≥12 years old

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Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← 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
				and consider short course of oral systemic corticosteroids	
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Moderate Persistent Asthma

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20 –39 yr 80%** **40 –59 yr 75%** **60 –80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/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% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		← 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 **(See figure 4–5 for treatment steps.)**		**Step 1**	**Step 2**	**Step 3** and consider short course of oral systemic corticosteroids	**Step 4 or 5**
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Asthma Control Classification Age ≥12 years old

	Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year	≥ 2 per year	

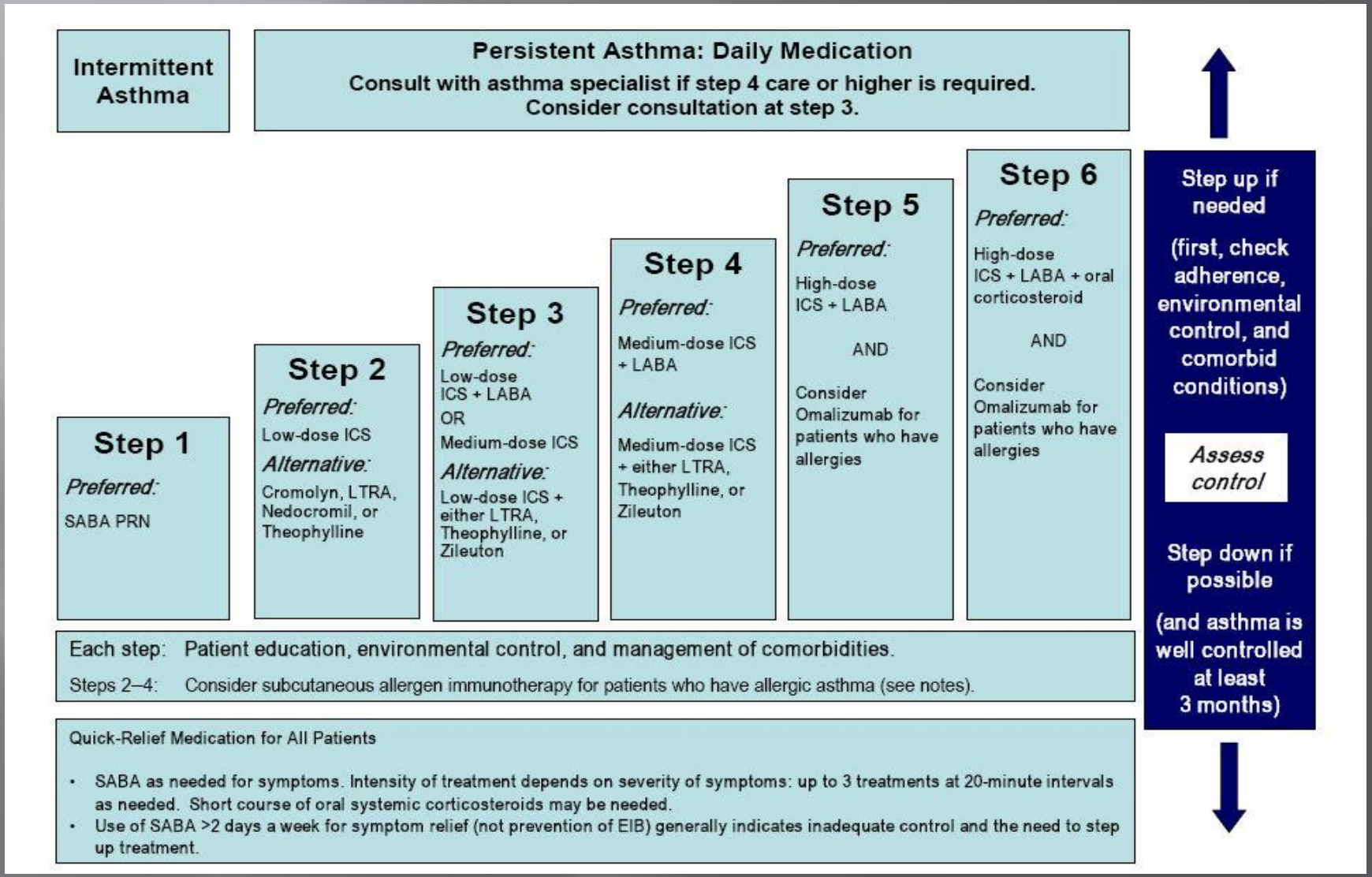
National Asthma Education and Prevention Program Guidelines Update. 2007.

Not Well Controlled Asthma

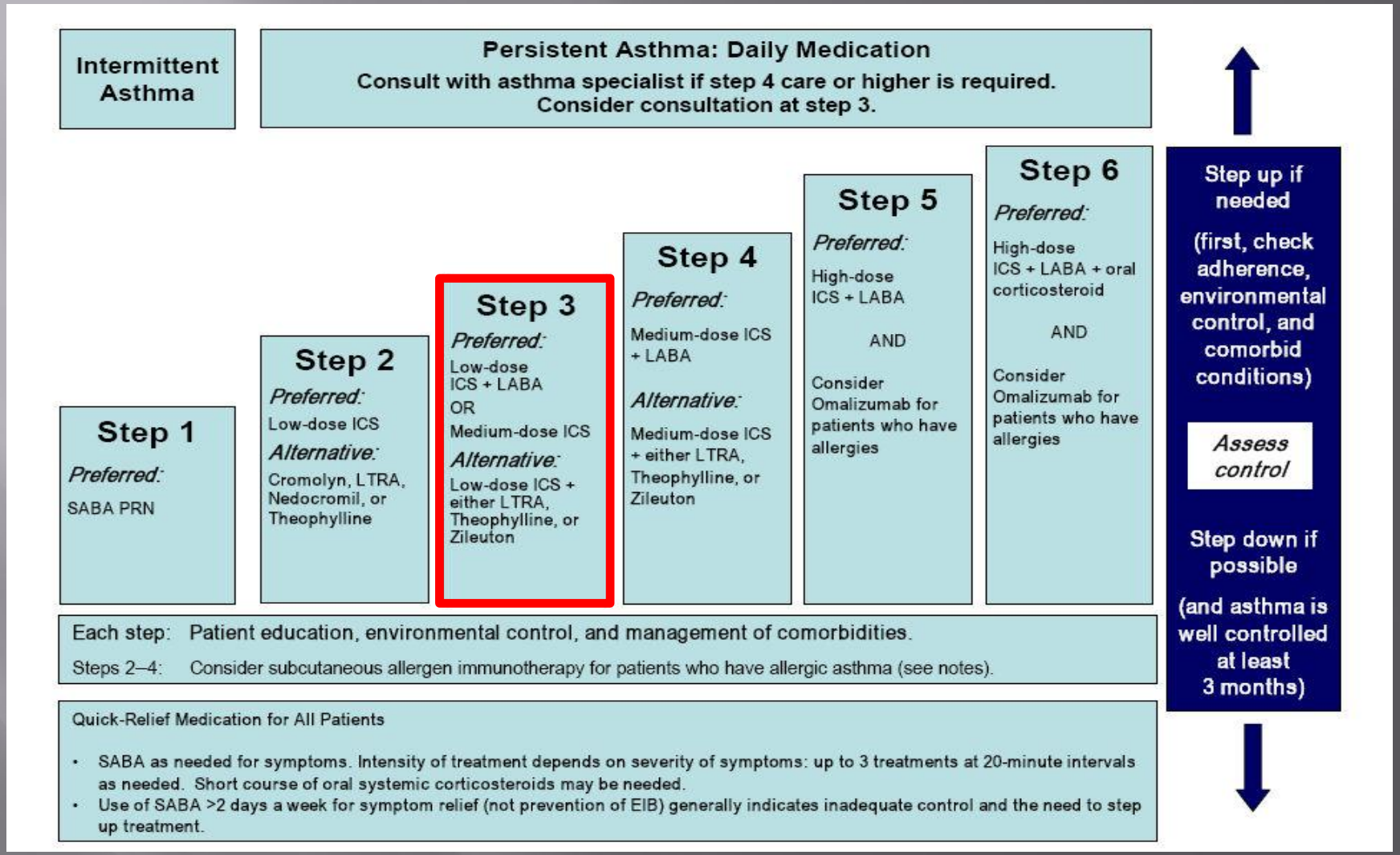
	Well Controlled	Not Well Controlled	Very Poorly Controlled
Daytime Symptoms	≤ 2 days/week	> 2 days/week	Throughout day
Nighttime symptoms	≤ 2x/month	1-3x/week	≥ 4x/week
SABA use	≤ 2 days/week	> 2 days/week	Multiple per day
Activity limitations	none	some	extreme
Oral steroid use per year	≤ 1 per year	≥ 2 per year	

National Asthma Education and Prevention Program Guidelines Update. 2007.

Treatment Approach



Step 3 Therapy



- Plan – Start on Low-dose ICS + LABA. Continue SABA PRN.

Case 4

- A patient comes to see you after having issues with his asthma for many years. He has been having use of his albuterol daily. He has been put on mometasone furoate and formoterol fumarate dihydrate 200/5 mcg two puffs BID and after review of his technique is taking both of these medications well. He was also put on tiotropium bromide 1.25 mcg two puff qday. He says that his sx get much worse in the spring and fall seasons. He will go to the ED at least one in each of these seasons.
  - FEV_1 – 1.3 L (72%)
  - FVC – 2.0 L (89%)
  - FEV_1/FVC – 65 %

- What do you do next for this patient?

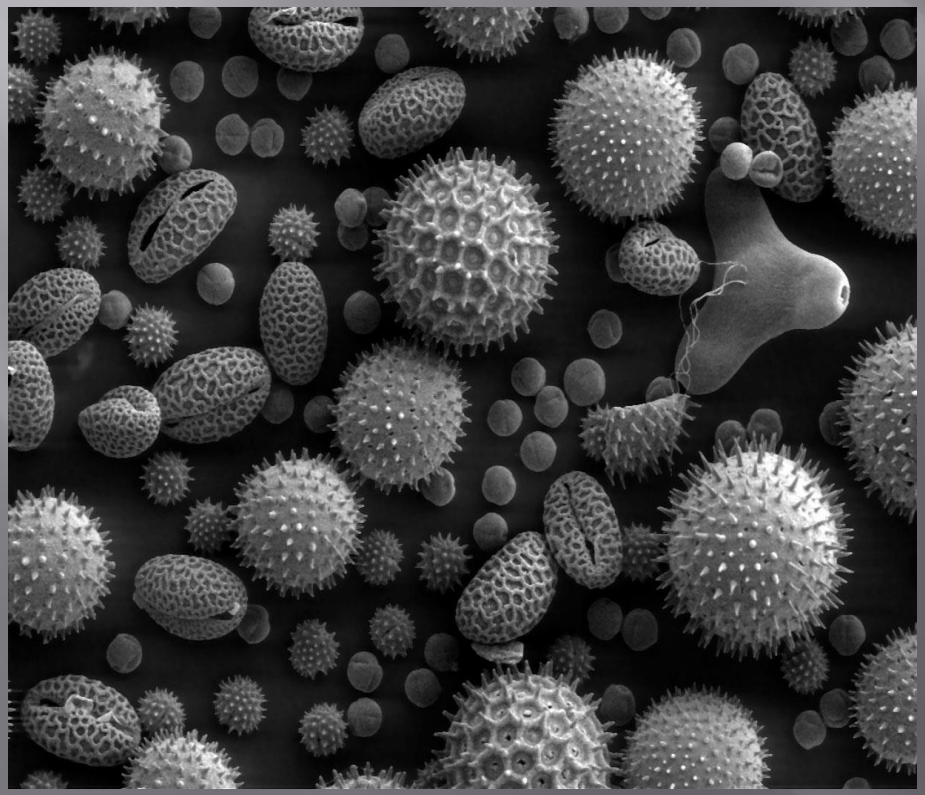
New develops that have been published since the guidelines have been published:

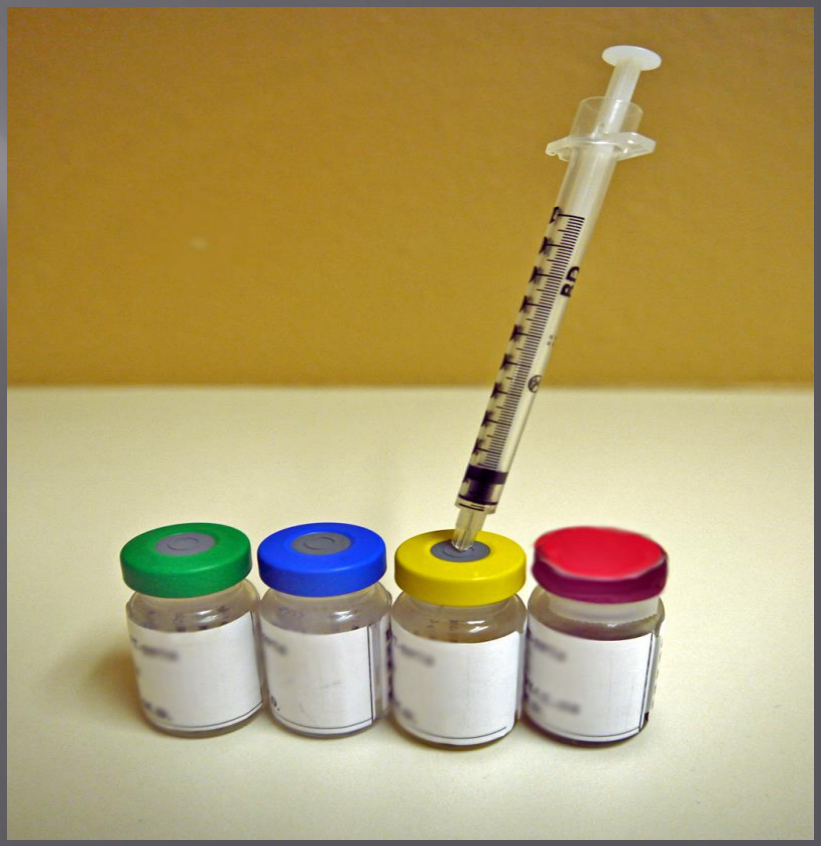
- Tiotropium Bromide can be added in place of a LABA to a moderate to high dose of ICS if the patient is not controlled or to a ICS/LABA combination for poor control
- Ipratropium bromide can be used in the ED when albuterol use in maximized and patient still has symptoms. This may decrease risk for hospitalization.

Other Control Modalities

Other Modalities for Treatment of Asthma

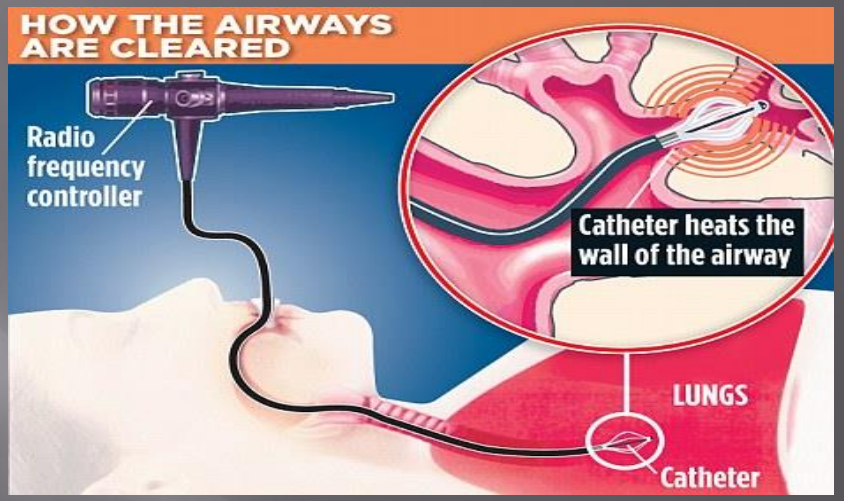
- Allergy Immunotherapy
  - Used to control seasonal and perennial triggers of asthma
  - Current mechanism is not totally understood and remains controversial



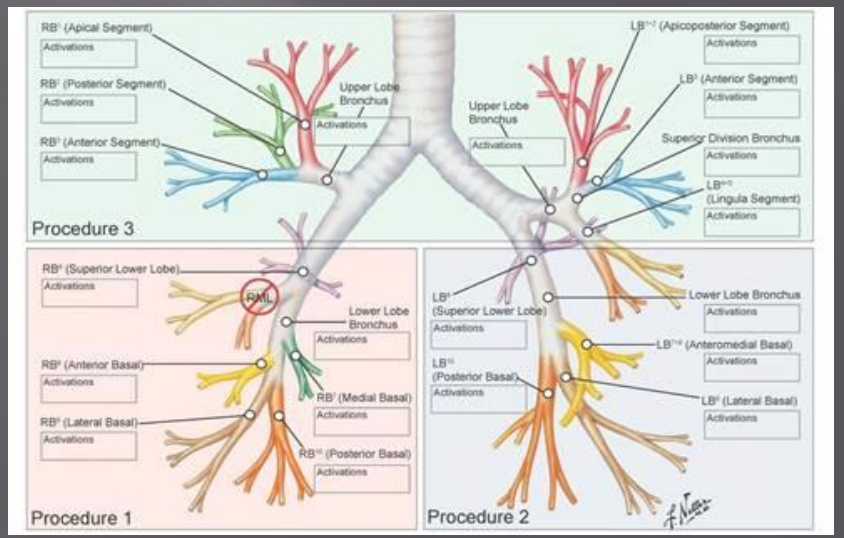


Other Modalities for Treatment of Asthma

- Bronchial Thermoplasty
  - Treatment for severe asthma approved by the FDA in 2010 for 18 years and older who do not have control on ICS
    - Delivery of controlled, therapeutic radiofrequency energy to the airway wall, thus reducing the amount of smooth muscle present in the airway.



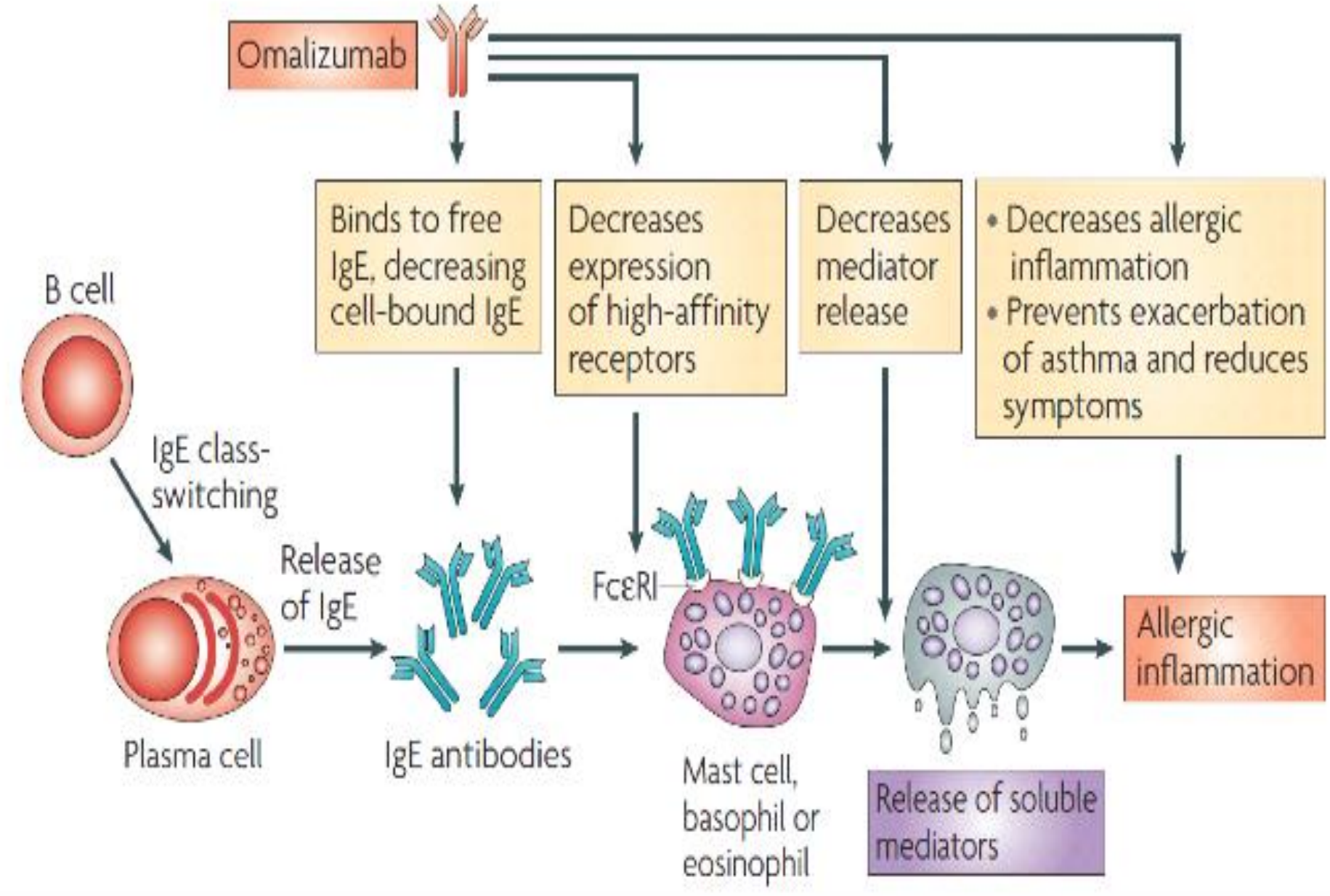
- AIRE-2 study
  - Marked decrease in ED visits, severe exacerbations, and lost work or school time
    - Significant at trial completion and 5 year follow-up



Biologics

"Older" Approved treatments

- Omalizumab
  - Recombinant humanized anti-IgE monoclonal antibody that binds Fc portion of IgE leading to down-regulation of high-affinity IgE receptor on mast cells and basophils
  - Initial studies in severe atopic asthmatics (IgE level between 30 and 700 IU/ml) showing decreased exacerbations.
    - More recently high type 2 biomarkers (periostin, eosinophilia and FeNO) with significant decreased exacerbation rate
  - Cochrane review of 25 trials reported 26% exacerbation reduction vs 16% in placebo


Omalizumab
Binds to free IgE, decreasing cell-bound IgE
Decreases expression of high-affinity receptors
Decreases mediator release
• Decreases allergic inflammation
• Prevents exacerbation of asthma and reduces symptoms
B cell
IgE class-switching
Plasma cell
Release of IgE
IgE antibodies
FcεRI
Mast cell, basophil or eosinophil
Release of soluble mediators
Allergic inflammation

"Newer" Approved Treatments

- IL-5 targeted therapies
  - Currently 3 monoclonal antibodies, approved or under development, that target IL-5-mediated inflammation
    - Mepolizumab
    - Reslizumab
    - Benralizumab
  - Blood eosinophil counts are ideally obtained before oral corticosteroids and high-dose inhaled steroids

IL-5 Targeted Therapies

- Mepolizumab (SC)
  - FDA approved for eosinophilic phenotype asthma
  - Considered an add-on maintenance therapy
  - Indicated for ages 12 and older
  - Mechanism of action: IgG1 antibody that antagonizes circulating IL-5
  - Administered subcutaneously 100mg every 4 weeks
  - Trial of severe asthmatics
    - Inclusion criteria
      - ≥880µg fluticasone or equivalent +/- another controller
      - ACQ≥1.5, ≥1 exacerbation (1 yr), FEV1 <80% + reversibility ≥12%
      - Serum eosinophils ≥150 at screening or ≥300cells/µL in past year
    - 47% reduction in all exacerbations
      - 61% reduction in all exacerbations requiring ED visit
  - Increased incidence of Herpes zoster infections, may consider vaccination before initiation

IL-5 Targeted Therapies

- Reslizumab (IV)
  - FDA approved for eosinophilic phenotype asthma
  - Indicated for ages 18 and older
  - Mechanism of action: IgG4 antibody that antagonizes circulating IL-5
  - Administered intravenously
    - 3mg/kg over 20-50 minutes every 4 weeks
  - Two exacerbation trials
    - Inclusion criteria
      - ≥440µg fluticasone or equivalent +/- another controller
      - ACQ≥1.5, ≥1 exacerbation (1 yr), FEV1 reversibility ≥12%
      - Serum eosinophils ≥400 cells/µL
    - Approximately 50% reduction in moderate exacerbations
    - 160ml improvement in FEV1 at 3mg/kg dose

IL-5 Targeted Therapies

- Benralizumab (SC)
  - FDA approved for eosinophilic phenotype asthma
  - Indicated for ages 18 and older
  - Mechanism of action: blocks IL-5 receptor
  - Administered subcutaneously
  - Dose-ranging study
    - Inclusion criteria
      - Medium-high dose ICS/LABA
      - 2-6 exacerbations past year
      - Eosinophilic phenotype by sputum or FeNO
    - 41% reduction in exacerbations in all patients
    - 57% reduction in patients with baseline eos >300cells/µL
      - FEV1 improvement of almost 200mL
  - Dose administered in ED with exacerbation
    - Approx 50% decrease in future exacerbations and 60% decreased hospitalization rate over subsequent 12 weeks.

IL-13

- IL-13 induces a wide range of negative effects including airway hyper-responsiveness, mucus production and increased IgE production

- IL-13 stimulates release of dipeptidyl peptidase-4 (DPP-4) and periostin, both of which are seen in higher levels in moderate to severe asthma
  - Both molecules could contribute to asthma pathogenesis

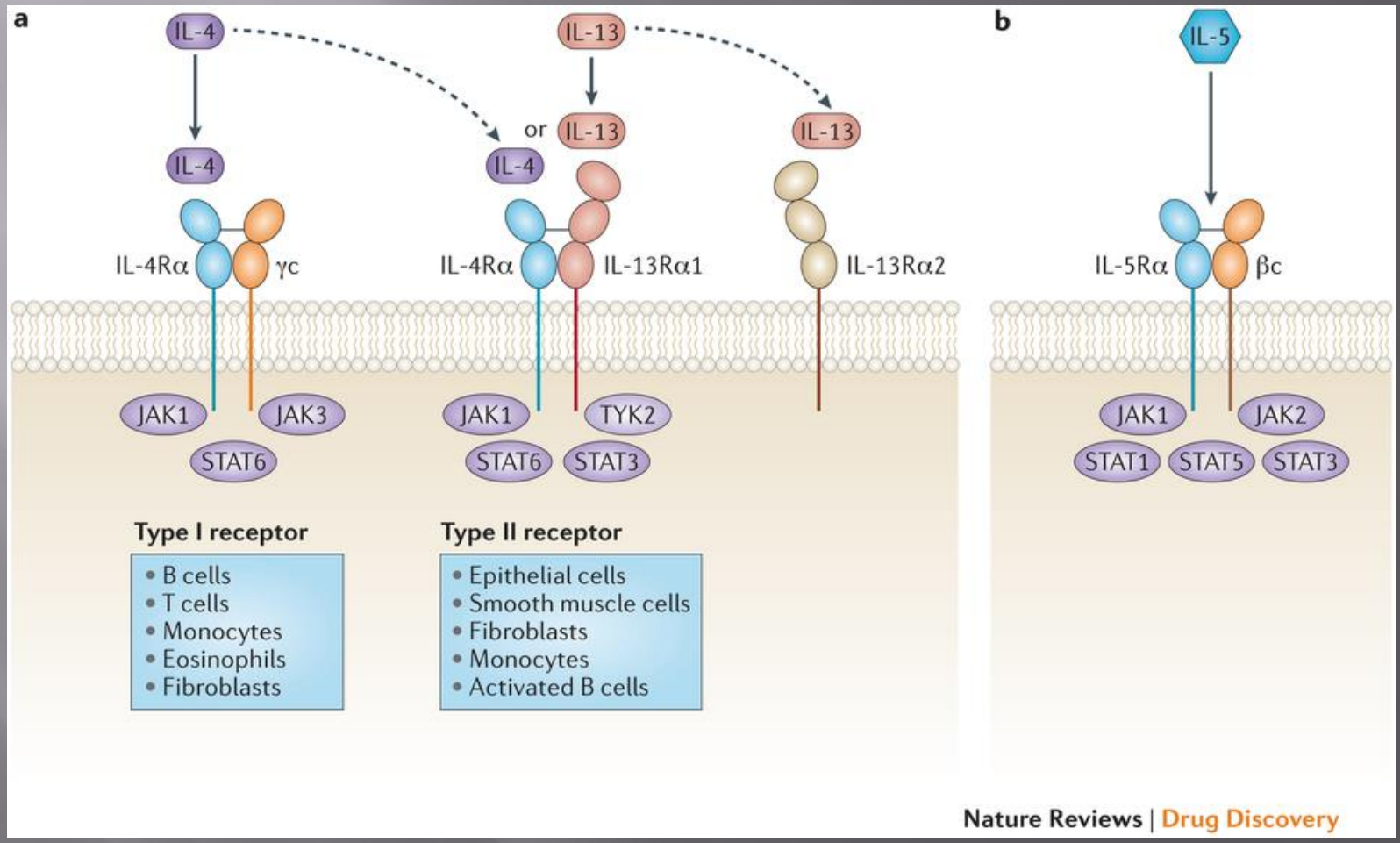
IL-13 Targeted Therapies

- Lebrikizumab
  - Mechanism of action: IL-13 antagonist
  - Administered subcutaneously
  - Early study
    - Inclusion criteria
      - 500-2000µg fluticsasone or equivalent + second controller
      - ACQ≥1.5, FEV1 40-80% predicted with reversibility ≥12%
    - 250mg monthly for 6 months
      - FEV1 improved 5.5% (8.2% in high periostin pts)
      - Improvement w/in 1 week and lasted 12 weeks after
  - Later study
    - 80% decrease in exacerbations in high blood periostin patients (>50ng/ml)
      - FEV1 increased by 9% as well

IL-13/IL-4 Targeted Therapies

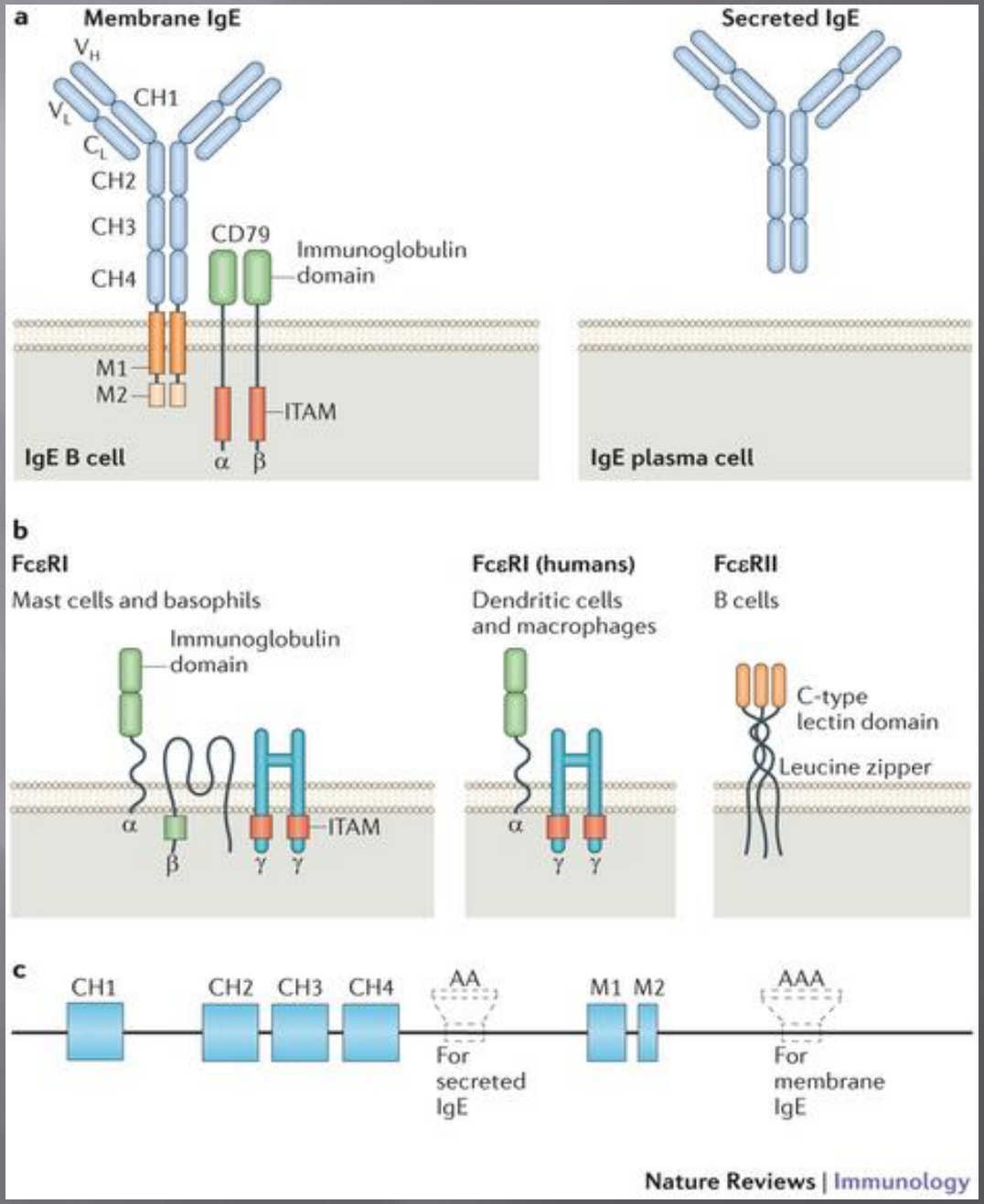
- Duilumab
  - Fully humanized monoclonal antibody
  - Mechanism of action: binds IL-4 α-receptor, involved in IL-4 and IL-13 signaling
  - Administered subcutaneously
  - Studied in patient with eosinophilia (>300 cells/μL) or sputum eosinophils >3%
  - Moderate to severe asthma study
    - Inclusion criteria
      - Medium-high dose ICS
      - One exacerbation in past 2 years
      - Serum eosinophils ≥300 cells/μL or ≥3% in sputum
    - Weekly administration at home
      - 87% decrease in exacerbations
      - Improved secondary measures of PFT, QoL, symptom score, SABA use and nocturnal awakenings
  - Phase 2b study
    - Biweekly self-administration
      - Improved lung function and decreased severe exacerbations

IL-4 & IL-13 Receptor Signaling



IgE Blockade

- Ligelizumab
  - Mechanism of action: high affinity anti-IgE humanized monoclonal antibody
    - Specifically targets M1 prime epitope of membrane IgE
    - Approximately 30 to 50-fold higher affinity for binding IgE compared to omalizumab


a
Membrane IgE
Secreted IgE
V_H
V_L
CH1
C_L
CH2
CH3
CH4
CD79
Immunoglobulin domain
M1
M2
ITAM
α
β
IgE B cell
IgE plasma cell
b
FcεRI
Mast cells and basophils
Immunoglobulin domain
α
β
γ
γ
ITAM
FcεRI (humans)
Dendritic cells and macrophages
α
γ
γ
FcεRII
B cells
C-type lectin domain
Leucine zipper
c
CH1
CH2
CH3
CH4
AA
For secreted IgE
M1
M2
AAA
For membrane IgE
Nature Reviews | Immunology

Other new developments that have been published since the guidelines have been published:

- Montelukast is not as effective as ISC, but compliance is better and for this reason over many years the benefits may be equal to ICS (NEJM)
- Montelukast is not as effective as adding LABA to ICS, but due to better compliance over many years the benefits may be equal to adding LABA to ICS (NEJM)
- Aerobic exercise is effective in reducing asthma symptoms
- Vitamin D deficiency is common in asthma and replacement may decrease steroid resistance.
- Adding macrolides may not be of significant benefit in most asthma patients

Assessing Asthma Control: "Rules of Two"

- If the answer to following questions is yes, a long term controller may be needed or you need to increase care
  - Do you take your quick relief inhaler more than TWO TIMES A WEEK?
  - Do you awaken at night with asthma more than TWO TIMES A MONTH?
  - Do you have daytime symptoms more than twice a week?
  - Do you have attacks more than twice a year
  - OR is there any limitation on exercise or QOL

Summary: what is stressed in the guidelines

- Severity classification on first visit.
- Asthma control on subsequent visits.
- Different guidelines for ages 0 to 4, 5 to 12 and greater than 12.
- Addition of functional ability and exacerbations to both severity and control.
- Stresses that ICS are the drug of first choice.
- Addition of omalizumab or mepolizamab for severe uncontrolled asthma.
- Addition of zileutin for moderate asthma.
- Increase importance of prednisone for severe asthma and very poorly controlled asthma

Conclusions

- Recognize the goals of the National Asthma Education and Prevention Program (NAEPP)
- Properly classification according to the latest National Heart, Lung and Blood: Expert Panel Report 3 (EPR3)
  - **http://www.nhlbi.nih.gov/guidelines/asthma/**
- Recognize proper therapy and how to step-up and *step-down* the current medications available for asthma control
- New biological medication that will be used and "tailored" to moderate to severe asthmatics when mainstay inhalers do not allow adequate control.