S (MART) Therapies for Asthma

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Disclosures and Conflict of Interest

None

Objectives

- Discuss asthma phenotypes and specific therapies
- Review current recommendations in updated National Asthma Education and Prevention Program and GINA guidelines
- Review S(MART) therapy for asthma

What is asthma?

NHLBI 2007

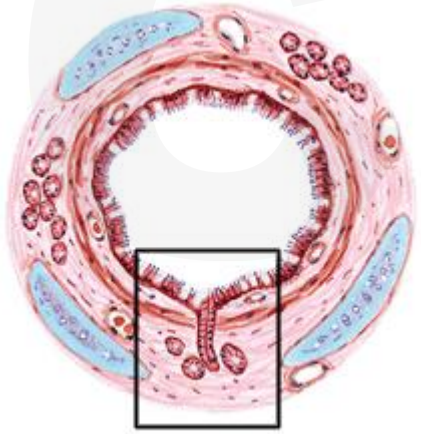
"a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma" (10).

What is asthma?

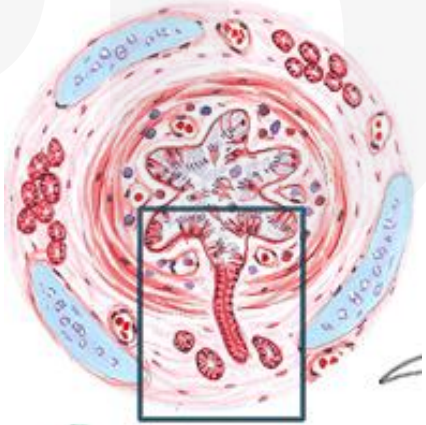
GINA 2019

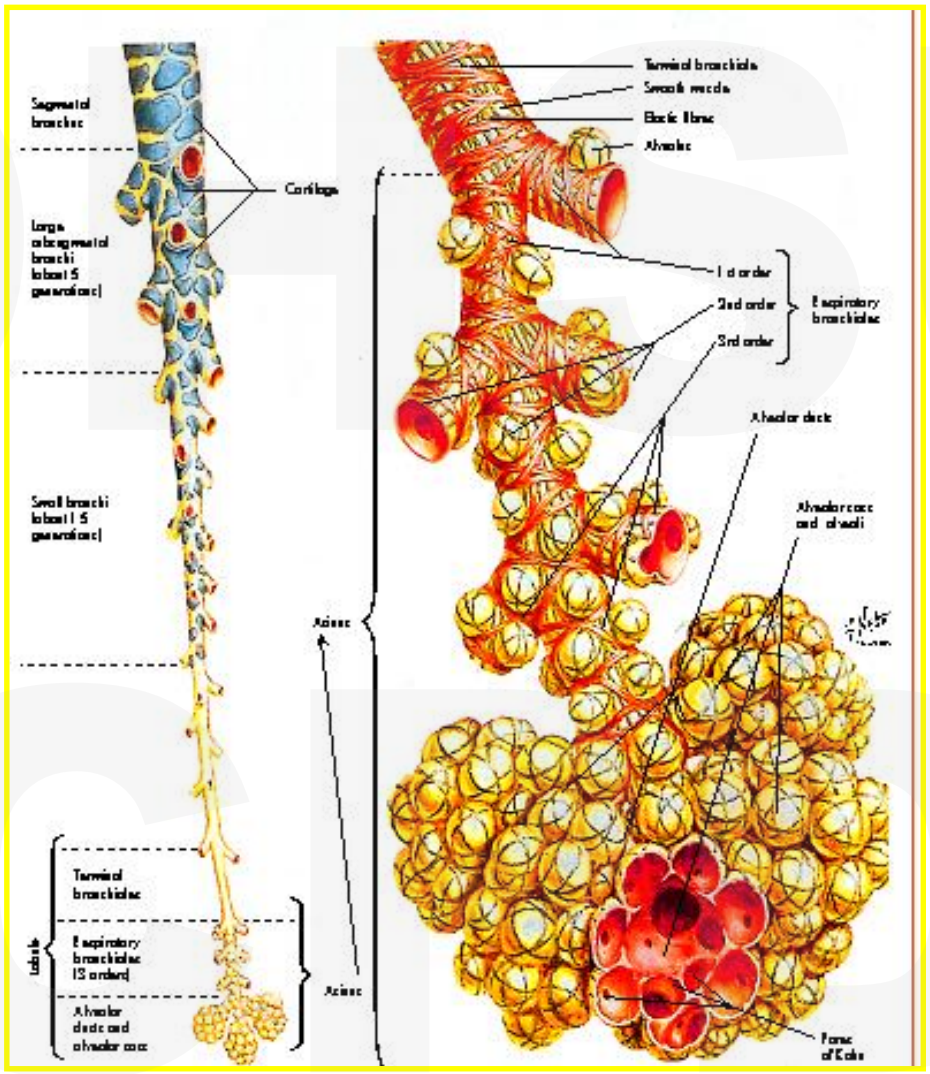
"a heterogenous disease, usually characterized by chronic airway inflammation defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitations."

Normal Airway

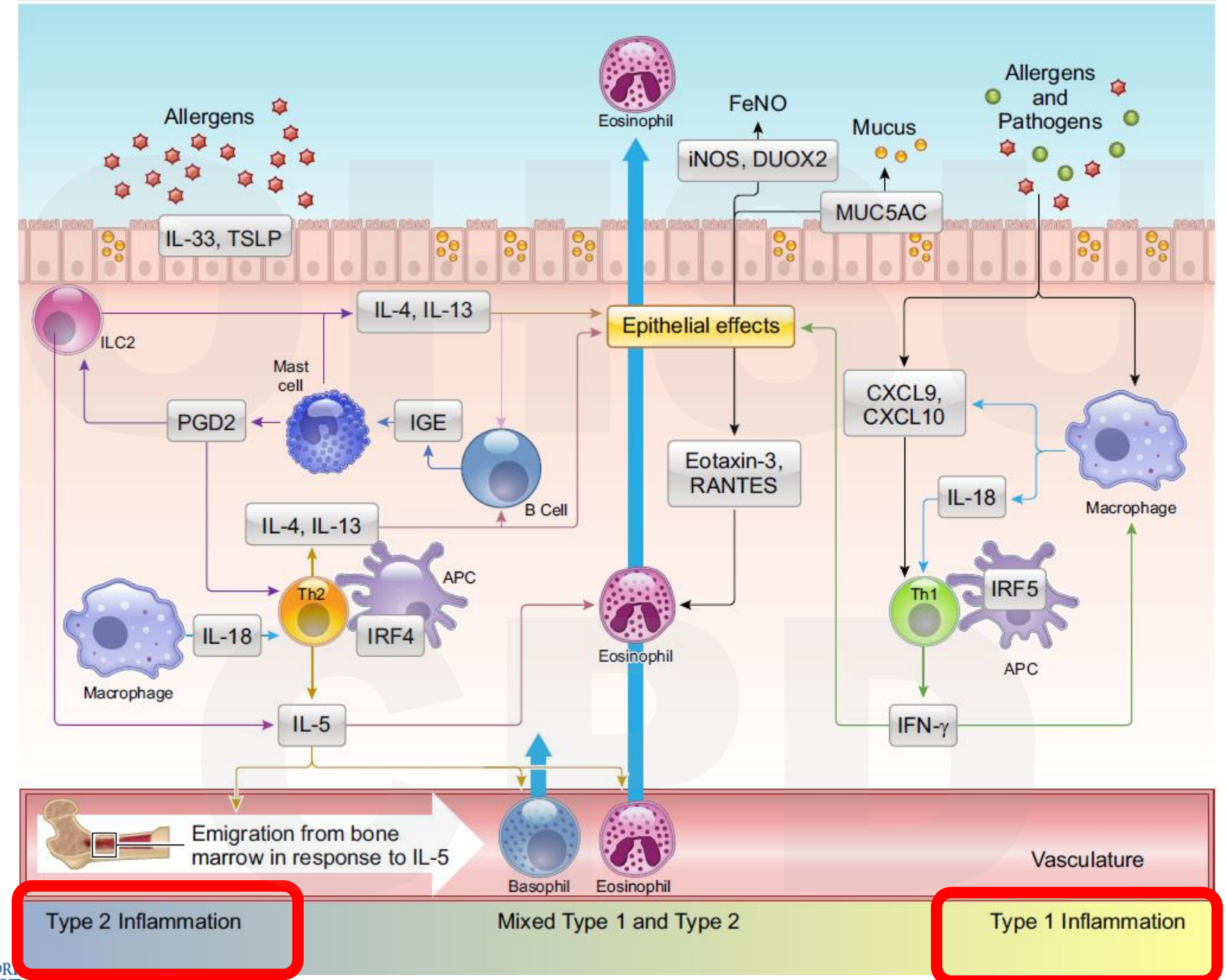


Asthma

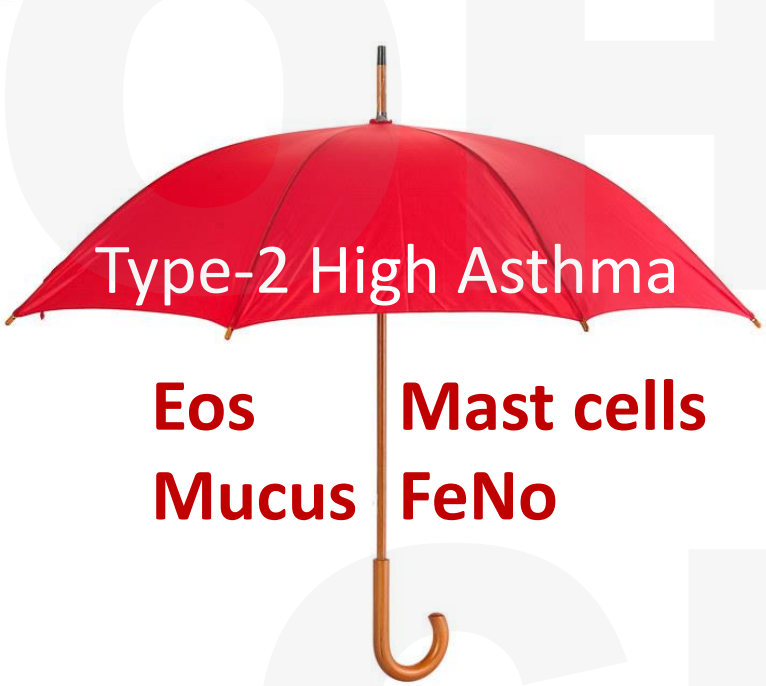


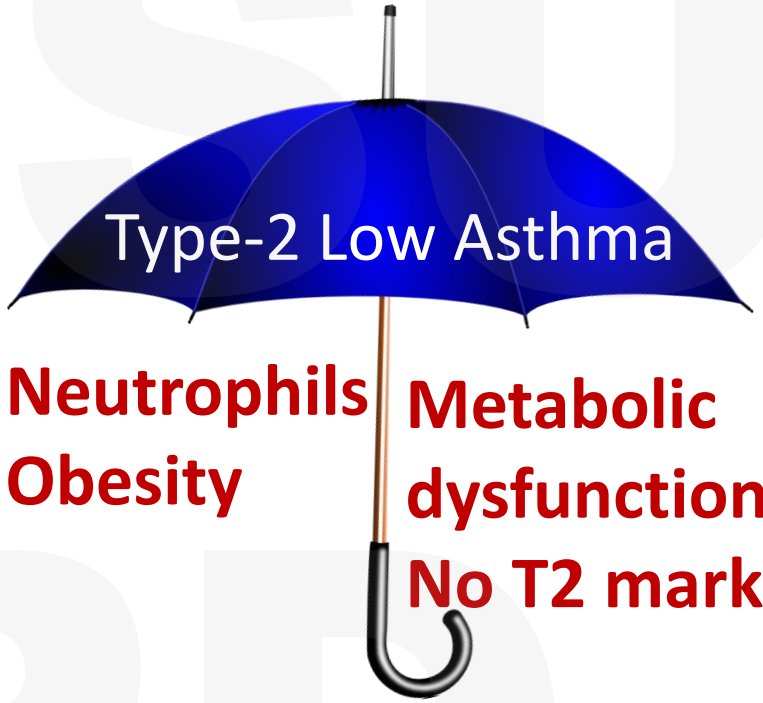


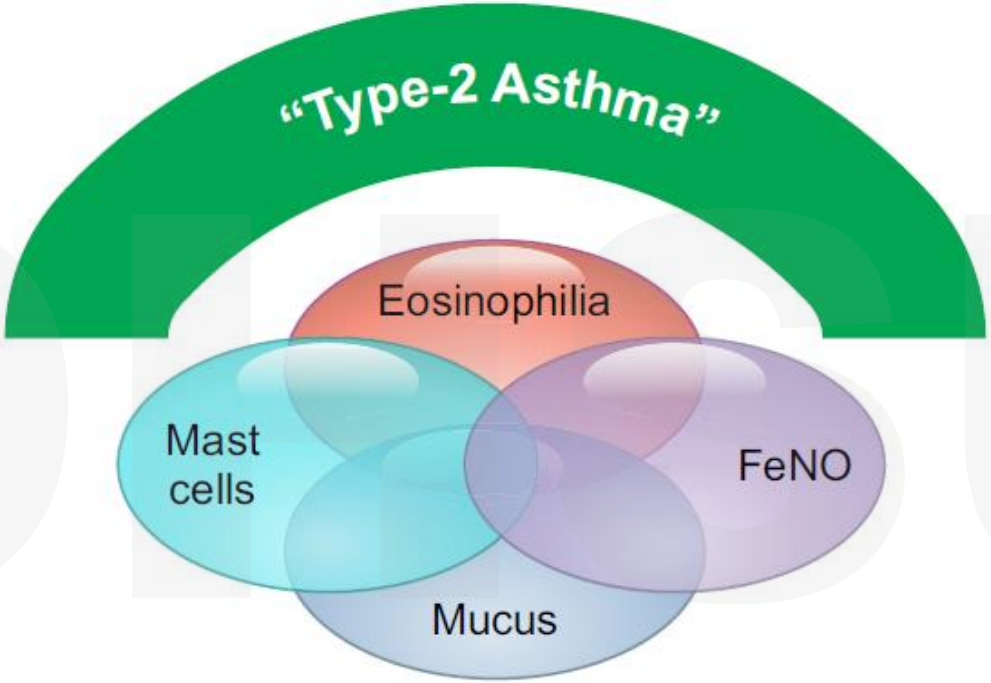
Source: Creative Commons



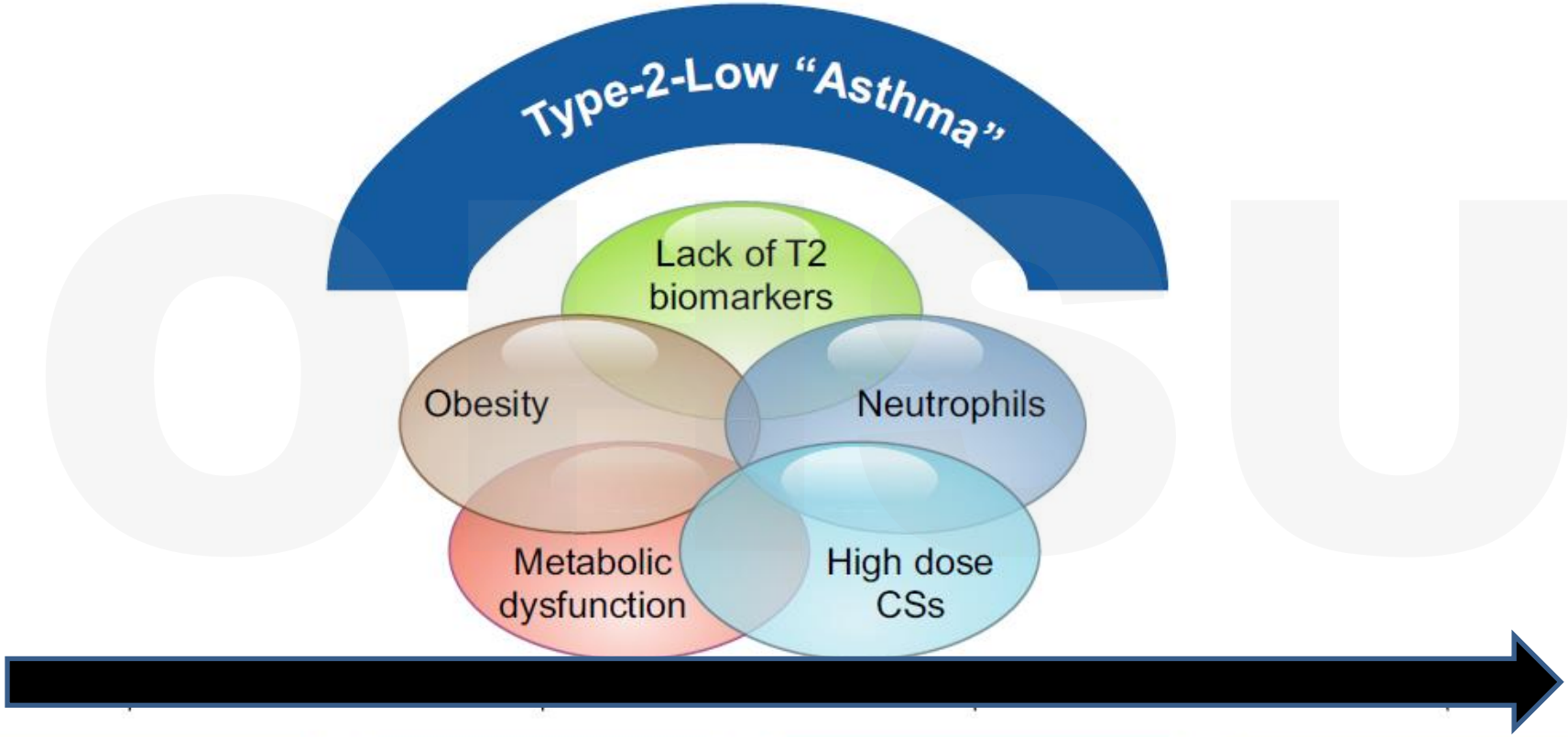
Ray et al., 2020, *Physiol Rev* 100: 983–1017







Mild CS responsive early onset allergic asthma	Early onset, moderate-severe CS treated-modestly responsive allergic asthma	Late onset eosinophilic Moderate-severe/ less CS responsive Nasal polyposis	Complex T2 Very severe, T cell/Type-1 dominant autoimmunity
Mediators: IL-4, 13, IgE	**Mediators**: IL-4, 13, IL-5, IgE	**Mediators**: IL-4, 5,13, leukotrienes	**Mediators**: IL-4,5,13 IFNγ
Rx: ICS	**Rx**: CSs,Anti-IgE/anti-IL4R	**Rx**: CSs, Anti IL-4R/Anti-IL-5/5R	**Rx**: Anti-IL4R/Anti-IL-5/5R with/without alternative immunosuppressive



Stable mild asthma
Intermittent obstruction
Mediators: mast cell related?

Rx: bronchodilators/low dose ICS?

Late onset obese airway disease
minimal obstruction and reversibility
Mediators: IL-6, IL-1β

Rx: weight loss/metabolic targets, Anti-IL-6?

Early onset,
long disease duration
high dose CS Rx
moderate obstruction/minimal BD response
Mediators: unknown

Rx: unclear/thermoplasty?

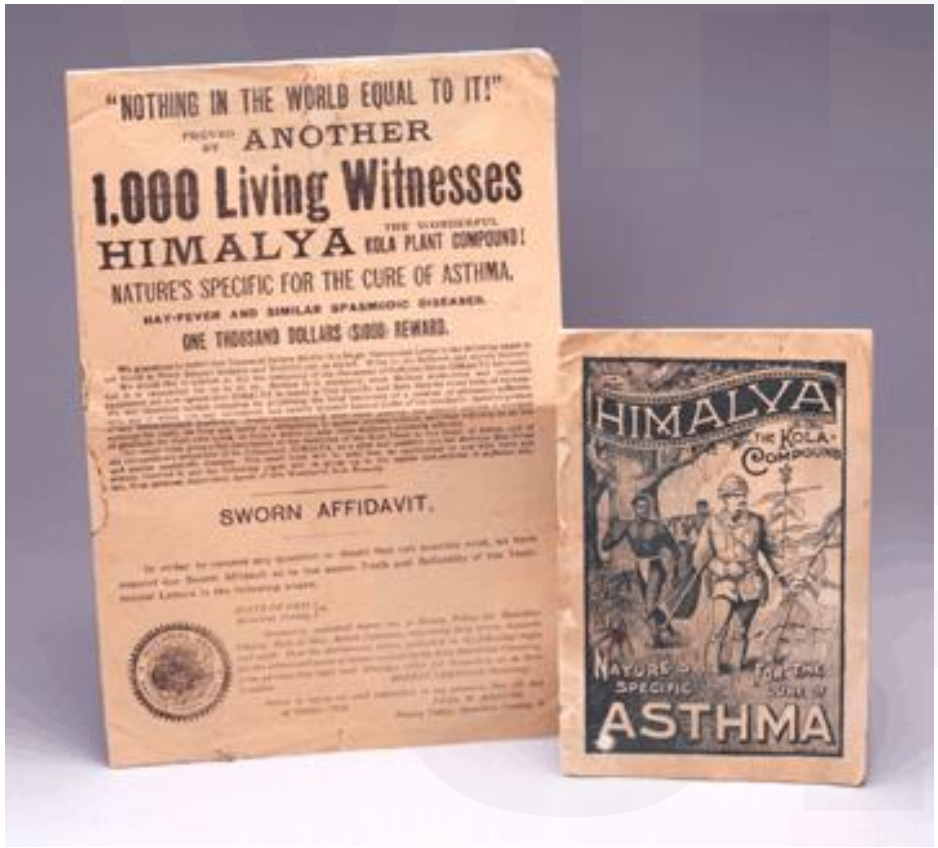
Late onset,
infection/smoking
Sputum production/moderate obstruction
Mediators: Neutrophilic/ inflammasome

Rx: macrolides?, anti-IL-1β? Mucus clearance measures

Objectives

Review current recommendations in updated National Asthma Education and Prevention Program and GINA guidelines

Once upon a time….



Asthma Guidelines

- National Asthma Education And Prevention Program (NAEPP)
- Global Initiative for asthma (GINA)

National Asthma Education And Prevention Program

NAEPP

- Started 1989
  - Federal Program
- Initial Guideline 1991
- Revisions
  - 1997, 2002, 2007, and 2020

Global Initiative for Asthma

GINA

- Launched 1993:
  - National Heart, Lung and Blood Institute
  - National Institutes of Health
  - World Health Organization
- Since 2014 funded entirely by the sale of its documents and resources.
- Guidelines updated annually!

How to use the Guidelines?

"The diagrams are intended to help clinicians integrate the new recommendations into clinical care, and are meant to assist, and not replace, clinical judgment or decision-making for individual patient management, with input from individuals with asthma about their preferences"

What are the Benefits?

- Standardization of care based on best available evidence
- Easier to follow for patients
- Improved asthma control
- Decreased use oral steroids
- Fewer severe asthma exacerbations requiring ED visit or hospital care

Case # 1

- 3 year old with intermittent asthma
- Albuterol as needed once every other month during the summer
- Started preschool 2 weeks ago and now has cold with runny nose, cough. No wheezing.
- Parents call advice nurse at your office.

Case # 1

- What do you recommend to the parent?
- New Recommendation:
  - 7-10 day course of daily inhaled steroid.
  - PRN Albuterol

Case # 1

Children ages 0–4 years who have had three or more episodes of wheezing triggered by respiratory tract infections in their lifetime or who have had two such episodes in the past year and are asymptomatic between respiratory tract infections.

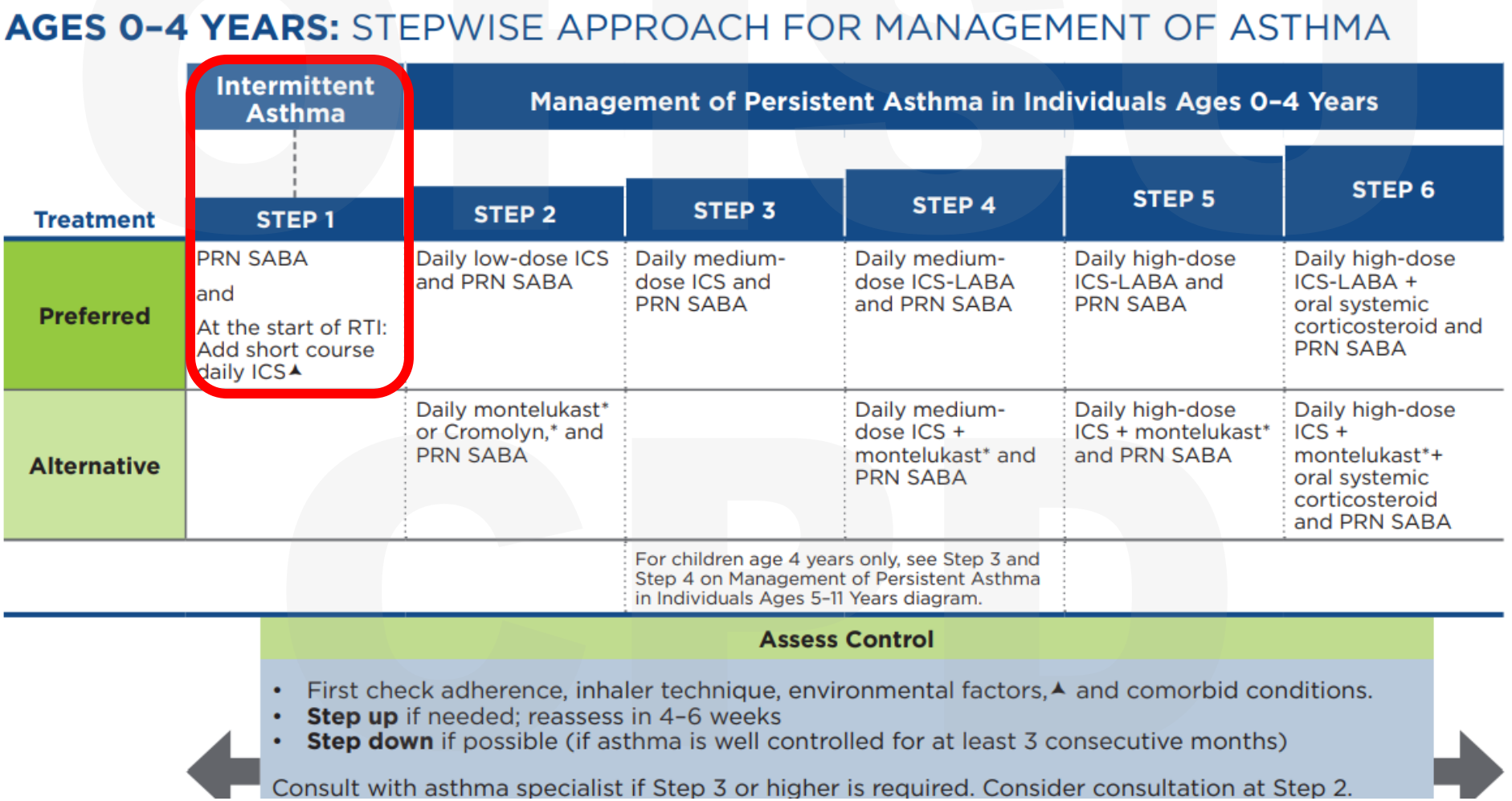
Note: absence of the word asthma.

Case # 1

- Budesonide inhalation suspension, 1 mg, twice daily for 7 days at the first sign of respiratory tract infection-associated symptoms.

- Caregivers can start intermittent ICS treatment at home without a visit to a health care provider when they have clear instructions.

Case # 1



Case # 2

- 3 year old with intermittent asthma
- Albuterol as needed once every other month during the summer
- Started preschool 2 weeks ago and now runny nose, cough and wheezing. Mild retractions and needing Albuterol every 4 hours for > 24 hours
- Parents call advice nurse at your office.

Case # 2

- What do you recommend to the parent?
- Start oral steroid
- Albuterol

Exacerbation management

- If needing Albuterol or ICS-formoterol more often than every 4 hours
- Retractions or wheezing not resolving or improving after rescue inhaler
- Needing rescue inhaler q 4 more than 3-4 x per day

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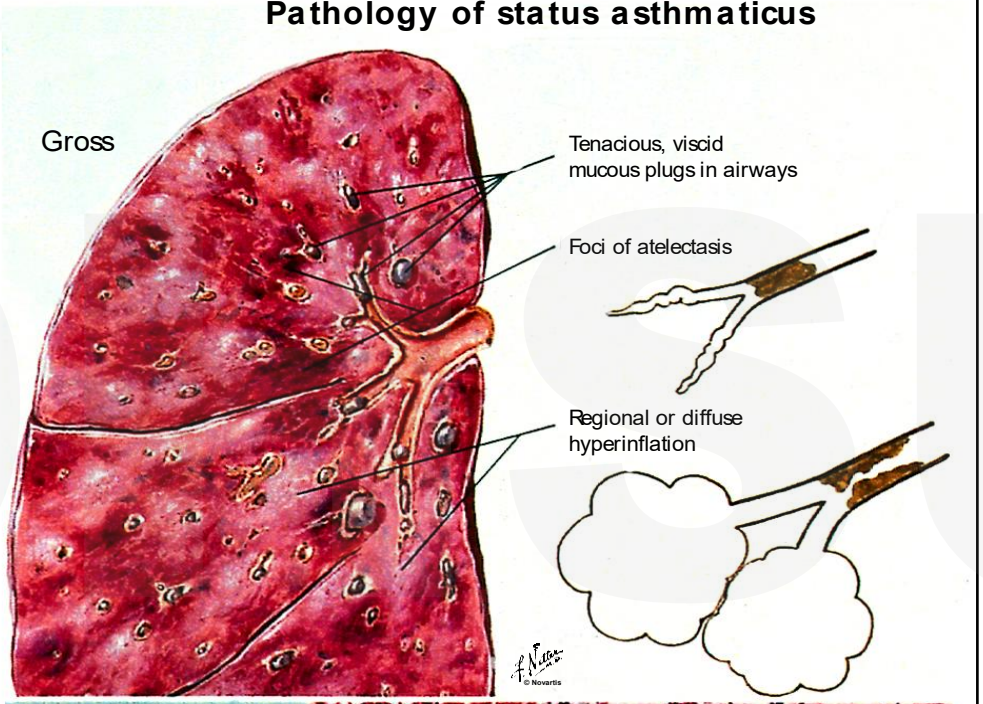
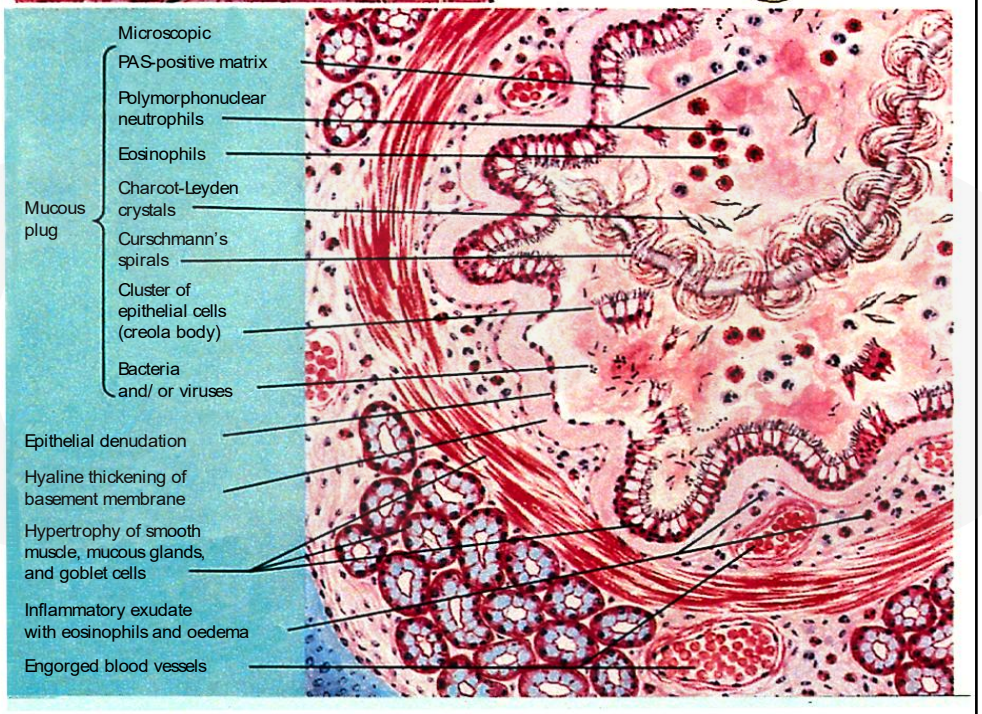
Pathology of status asthmaticus





Oral steroids

Every child with asthma should have prescription for a course of oral steroids at home with instructions on when to use

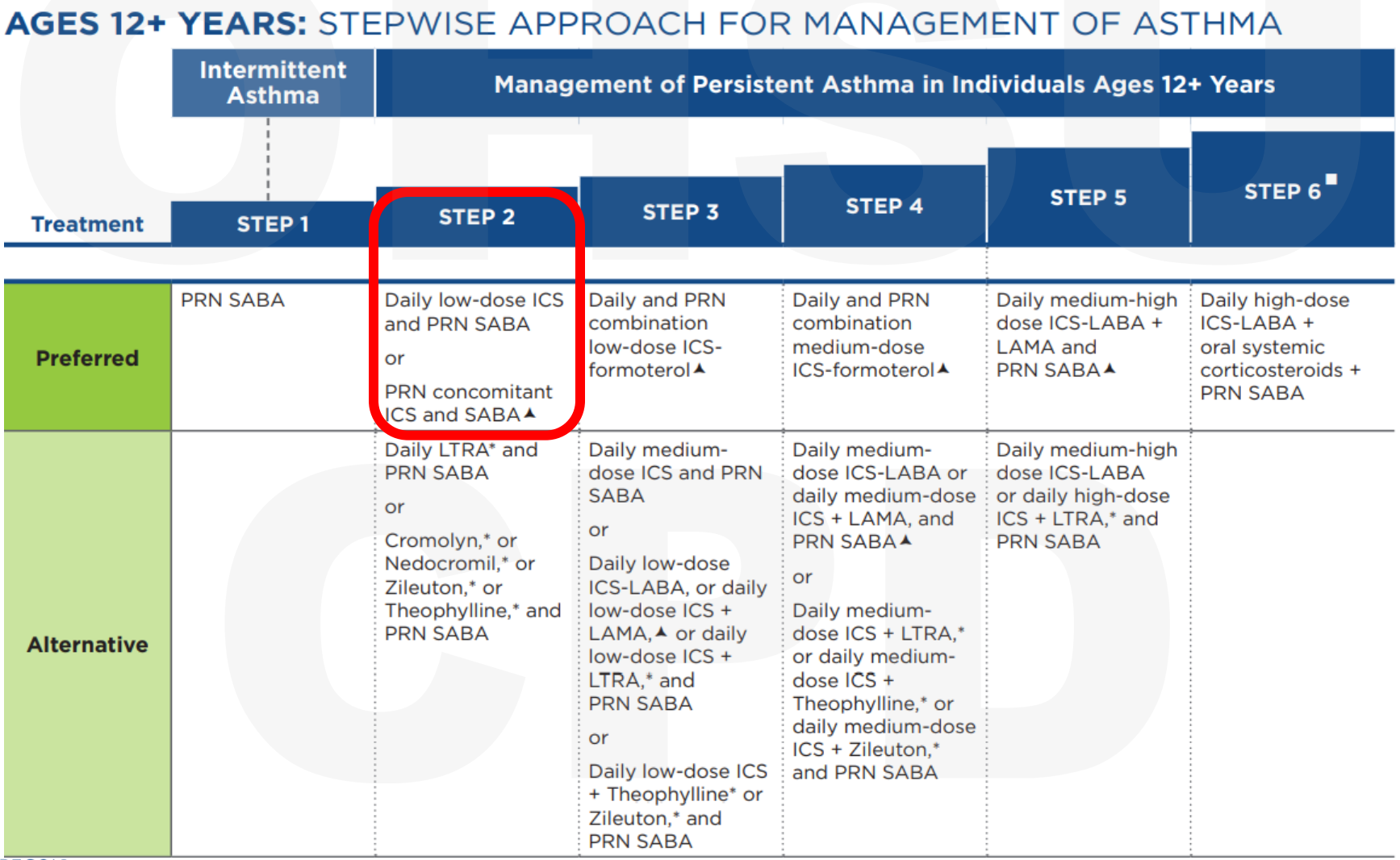
Case # 3

- You are seeing a 14 year old child with mild persistent asthma
- At baseline rare Albuterol use on low dose inhaled steroid
- Parents learned from Instagram post that there are new asthma recommendations

Case # 3

- What do you recommend to the parent?
- They can keep going with ICS + PRN Albuterol or
- They can change to PRN Albuterol + ICS

Case # 3


AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA
Intermittent Asthma
Management of Persistent Asthma in Individuals Ages 12+ Years
Treatment
STEP 1
STEP 2
STEP 3
STEP 4
STEP 5
STEP 6
Preferred
PRN SABA
Daily low-dose ICS and PRN SABA
or
PRN concomitant ICS and SABA▲
Daily and PRN combination low-dose ICS-formoterol▲
Daily and PRN combination medium-dose ICS-formoterol▲
Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲
Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative
Daily LTRA* and PRN SABA
or
Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA
Daily medium-dose ICS and PRN SABA
or
Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA
or
Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA
Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲
or
Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA
Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA

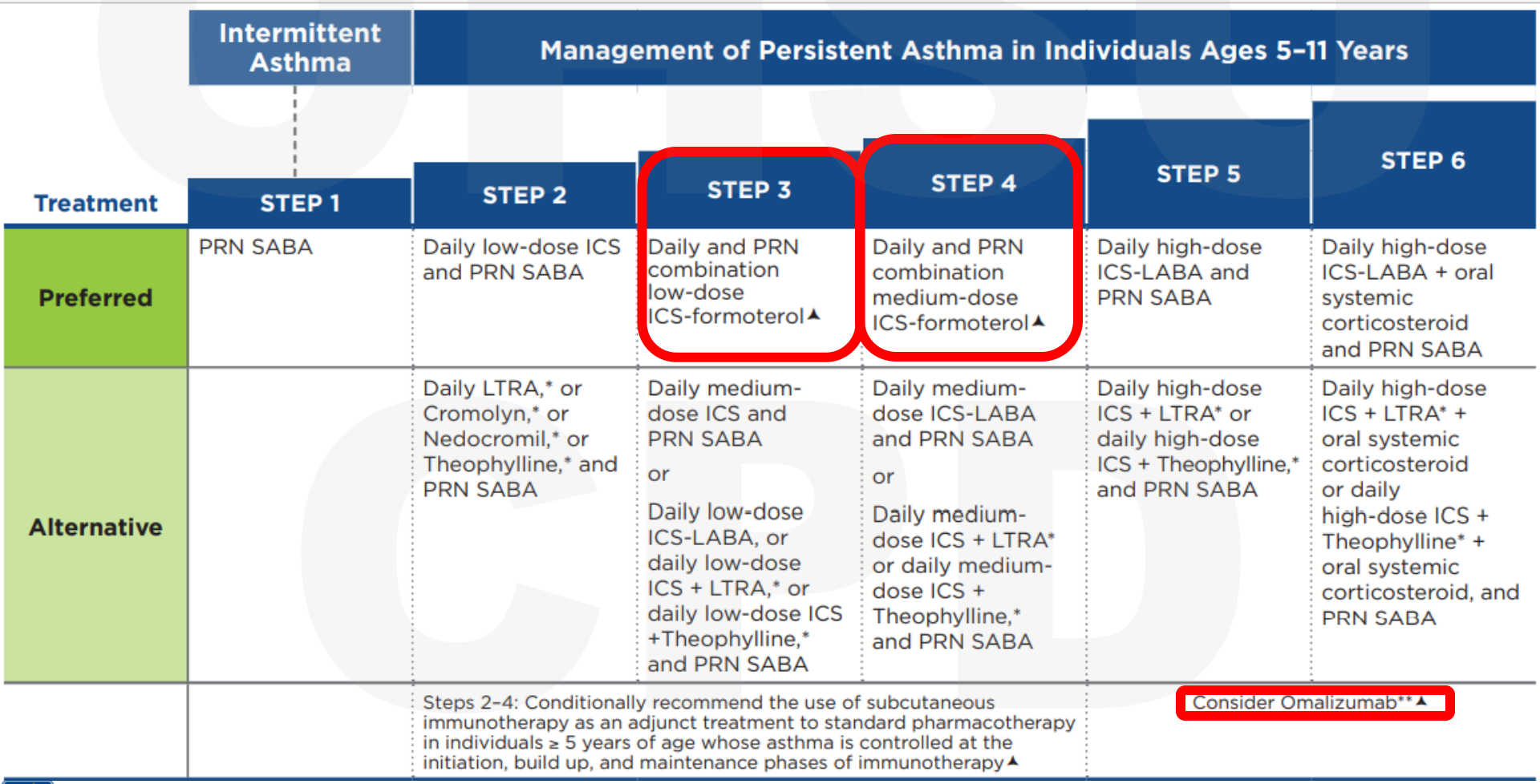
Case # 4

- 8 year old child with mild persistent asthma
- At baseline rare Albuterol use on low dose inhaled steroid
- Started school and has cough and wheezing episodes. Albuterol daily.
- Parents are calling nurse advice line

Case # 4

- What do you recommend to the parent?
- Consider stepping up therapy
- Now can consider SMART

Case # 4



	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider Omalizumab**▲	

Objectives

Review S(MART) therapy for asthma

S(MART) Therapy

Single (Maintenance And Reliever Therapy)

Step 3 and 4 care!

2025 GINA Guideline also step 1 or 2 if > 12 years of age

Rationale

- Albuterol is a muscle relaxant
- Asthma is an inflammatory disorder
- Inhaled steroids are anti-inflammatory
- It makes sense to increase anti-inflammatory therapy in addition to bronchodilation

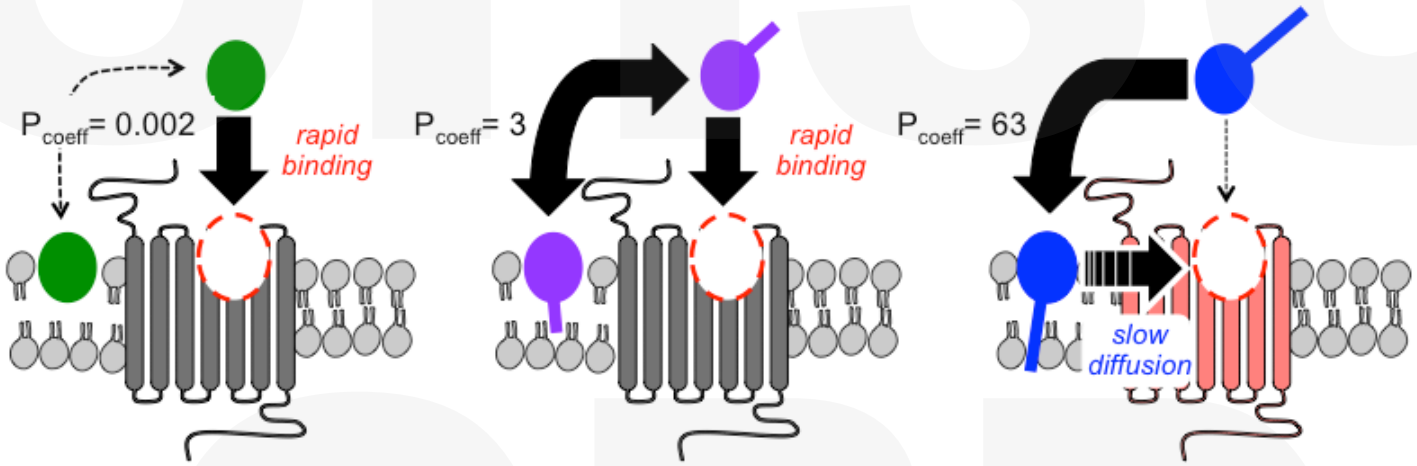
SMART
Budesonide-formoterol dosing

		Step 3		Step 4		Step 3 or 4 max daily inhalations
Age	Dose	Maintenance	PRN	Maintenance	PRN	
≥12 years	160/4.5	1 inh BID or 1 inh qday	1 inh PRN	2 inh BID or 1 inh BID	2 inh PRN	12
4-11 years	80/4.5	1 inh daily	1 inh PRN	1 inh BID	1 inh PRN	8

Comparison Bronchodilators

Beta$_2$ Agonist Kinetics

Based on Anderson et al, 1994



Albuterol
- Hydrophilic
- Short duration (not stored in lipid)
- Rapid onset

Formoterol*
- Amphiphilic
- **Long duration** (retained by lipid)
- Rapid onset

Salmeterol*
- Lipophilic
- **Long duration** (retained by lipid)
- Slow onset (slow lipid diffusion to β_{2R})

Eur Respir J, 1994, 7, 569–578

(Example of action plan template for budesonide/formoterol.
A similar action plan could be constructed for other ICS/formoterol formulations, e.g. mometasone/formoterol)

My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol

Name: _____ Action plan provided by: _____

Date: _____ Doctor: _____

Usual best PEF: _____ L/min (*If used*) Doctor's phone: _____

Normal mode

My SMART Asthma Treatment is:

- ☐ budesonide/formoterol 160/4.5 (12 years or over)
- ☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

- I do not wake up at night or in the morning because of asthma

Other Instructions

_____

_____

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT** improving **OR**
- I am using more than 6 budesonide/formoterol relieve inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years)

I should:

- ☐ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms
- ☐ Start a course of prednisolone
- ☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____ mg prednisolone tablets per day for _____ days **OR**

_____

_____

If I need more than **12 budesonide/formoterol inhalations (total)** in any day, (or more than 8 inhalations for children 4-11 years) I **MUST** see my doctor or go to the hospital the same day

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations.

If I have any of the above danger signs, I should dial _ _ _ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion)
- If only albuterol is available, take 4 puffs as often as needed until help arrives
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack

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Downsides

- PRN versus daily controller can be confusing to some parents
- Patients with difficulty perceiving airflow obstruction may be under or over treated
- Requires effective education of parents and patients
  - Recommend “Teach Back”

Barriers to S(MART)

- Budesonide-formoterol not FDA approved for SMART therapy
  - US packaging: ≤4 puffs/day max

INDICATIONS AND USAGE

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Treatment of asthma in patients 6 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. (1.2)

Important limitations:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

Barriers to S(MART)

- Patients will need supply > 30 days
- Need for additional inhaler at school
- Cost
  - Albuterol is cheaper

Case # 5

- 8 year old child with moderate to severe asthma
- Currently taking medium inhaled ICS
- Parents come to clinic as they have heard something on their Facebook group about changes in asthma therapy.
- What do you recommend to that parents?

Case # 5

- Discuss changing to ICS-formoterol for control and as reliever (SMART-therapy)

Do not use ICS-formoterol as reliever if controller is ICS-salmeterol

Case # 6

- 8 year old child with moderate to severe asthma
- Currently taking ICS-Fomoterol + PRN Albuterol
- Asthma control worsening and needing Albuterol 1-2 x per day.
- What do you recommend to the parents?

Case # 6

- Discuss replacing PRN Albuterol with ICS-Formoterol (SMART) before stepping up.