Asthma 2022: The Age of Personalized Medicine is Upon Us

David Stukus, MD

Professor of Clinical Pediatrics

Division of Allergy and Immunology

Associate Program Director, Pediatric Allergy/Immunology Fellowship Training Program

Director, Food Allergy Treatment Center

Nationwide Children's

When your child needs a hospital, everything matters.℠

The Ohio State University

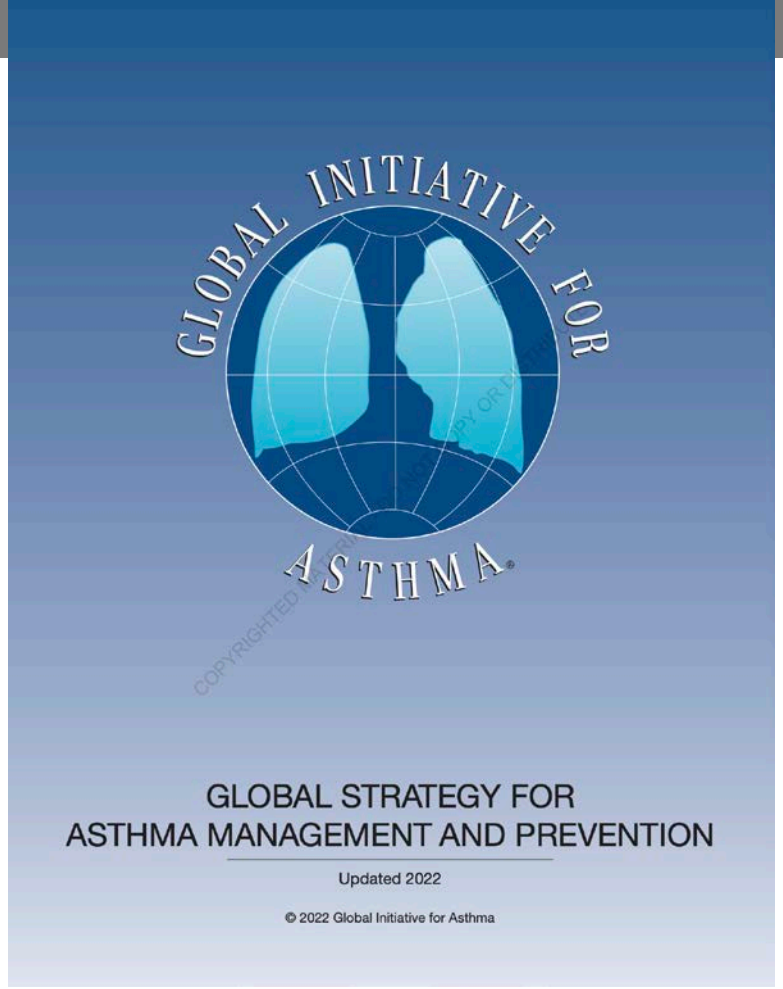
College of Medicine

Disclosures

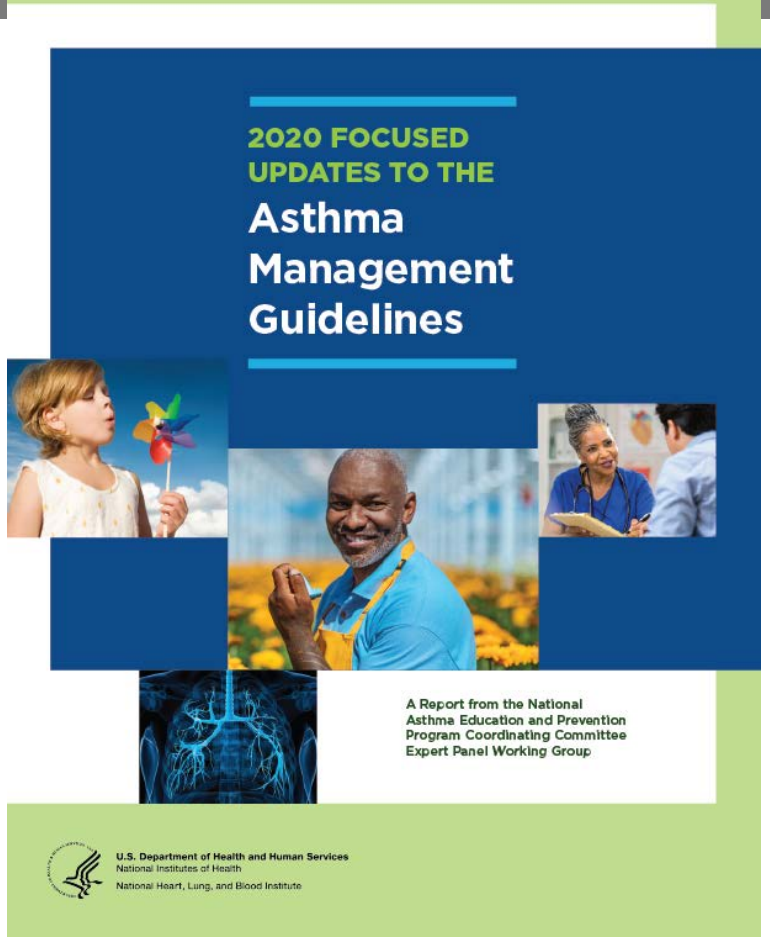
- Social Media Medical Editor – American Academy of Allergy, Asthma and Immunology
- Consultant –Before Brands, Kaleo, Novartis
- Associate Editor – Annals of Allergy, Asthma and Immunology
- Honoraria – ACAAI, AAP, AAAAI
- Non-financial:
  - Member – Joint Task Force on Practice Parameters for Allergy and Immunology
  - Member – Board of Regents, American College of Allergy, Asthma and Immunology

Objectives

- Identify key asthma phenotypes to assist management options
- Discuss new treatment options with families
- Assist families in identification of environmental influences



https://ginasthma.org/gina-reports/



https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Initial Thoughts…

- Asthma is a clinical diagnosis
- Often underdiagnosed
- Asthma is expected to change over time and throughout the year – so should management
- There are many treatment options available
- Treatment should be guided by phenotyping and shared decision making

Asthma is a Heterogeneous Disease

- Lower airway inflammation + recurrent episodes of reversible bronchoconstriction = asthma
- Every aspect of asthma is highly individualized
- There is no “one size fits all” approach
- Can present at any age
- Can be persistent and chronic OR infrequent and episodic
- Many children feel fine most days but experience sudden onset rapid exacerbations
  - Urgent health care utilization – ED/UC
  - Hospitalization

What is Your Diagnosis?

_____ year old with _____ episodes of persistent cough/wheeze/shortness of breath/difficulty breathing over _____ months. Symptoms do/do not improve after treatment with _____.

- Family history of asthma/allergies
- Personal history of allergies/atopic dermatitis

“Reactive Airway Disease” is NOT a Diagnosis

Pulmonary Perspective

“Reactive Airways Disease”
A Lazy Term of Uncertain Meaning That Should Be Abandoned

JOHN V. FAHY and PAUL M. O’BYRNE

Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco, California; and the Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Am J Respir Crit Care Med. 2001 Mar;163(4):822-3.

A

Thank you for your inquiry.

Unfortunately, I cannot give you a precise definition of reactive airways because such does not exist.

https://www.aaaai.org/allergist-resources/ask-the-expert/answers/old-ask-the-experts/reactive-airways-disease

Diagnosing Asthma in Young Children

- "Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present"
- Episodic: Do symptoms recur over time? (at least 4 episodes)
- Symptoms: Coughing, wheezing, difficulty breathing, shortness of breath
- Hyperresponsiveness: What has been the response to albuterol and/or systemic corticosteroids? If unknown, use as a diagnostic and therapeutic trial

What Does NOT Diagnose Asthma

- Pulmonary function tests
- Exhaled nitric oxide
- Physical exam

Each of these can be completely normal in a child with asthma

Each of these may look like asthma but be abnormal due to other causes

Asthma Predictive Index

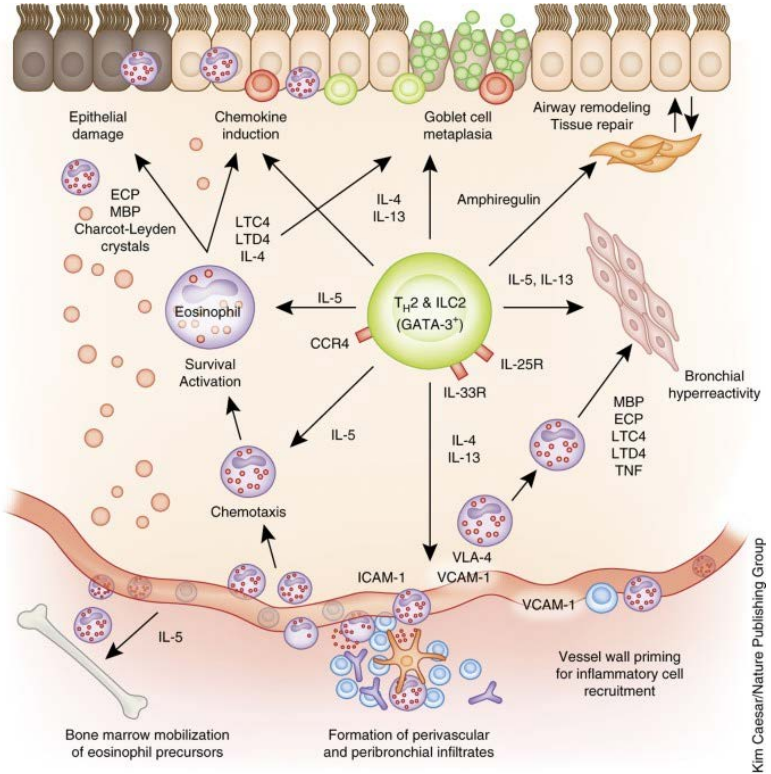
- Children 3 years old or younger
- 4 separate wheezing episodes in the past year

Major Criteria	Minor Criteria
Parent with asthma Physician diagnosis of atopic dermatitis Detectable IgE to aeroallergens	Physician diagnosed food allergies >4% blood eosinophils Wheezing apart from colds

- Prognostic…and now diagnostic tool?
- One MAJOR or TWO MINOR criteria = ~80% chance of persistent asthma at 7 years of age
- Zero criteria = very unlikely to have asthma

Pediatr Pulmonol. 2021 Oct;56(10):3183-3188.

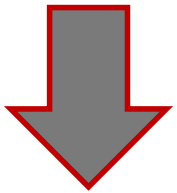
What Type of Asthma Is It?



The immunology of asthma. *Nat Immunol* **16,** 45–56 (2015).

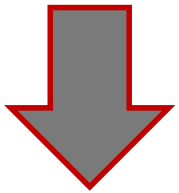
T2 Low vs. T2 High

- Neutrophil predominant
- Associated with late onset asthma, smoking and obesity



Less responsive to inhaled corticosteroids

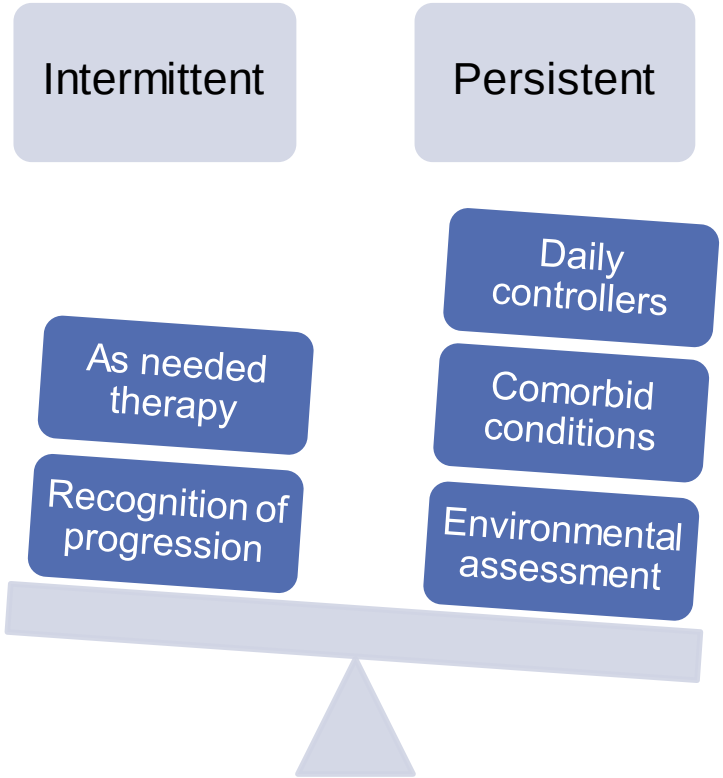
- Eosinophil predominant
- Associated with atopy, younger children



More responsive to inhaled corticosteroids

Clin Exp Allergy. 2017 Jul;47(7):848-855.

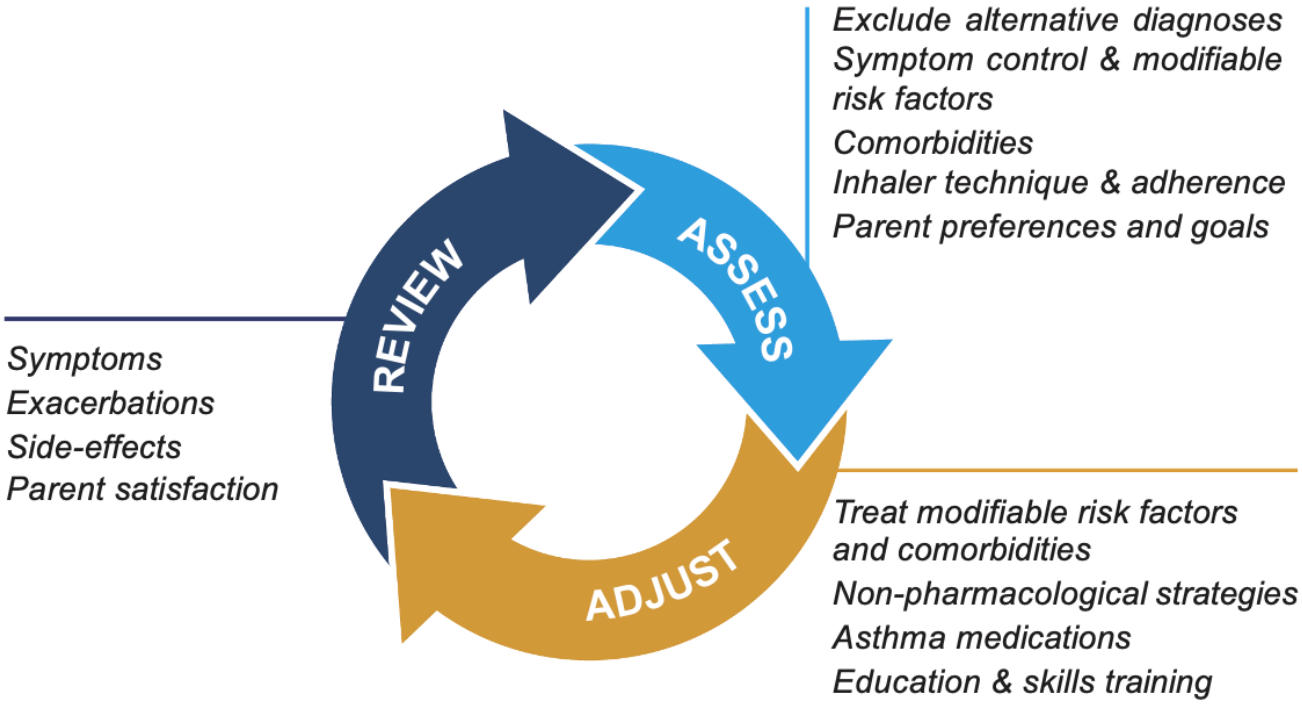
You've Diagnosed the "A Word"…Now What?



EVERYONE with asthma requires:

- Education
- Self-management skills
- Inhaler & spacer teaching
- Long term follow up
- Written treatment plans
- Fluid and dynamic treatment plans
- Support

The Never Ending Cycle of Asthma Management



https://ginasthma.org/gina-reports/

Common Asthma Triggers

- Upper respiratory infections
  - Autumn asthma spikes
- Weather changes
- Allergens
- Environmental irritants (pollution, ozone)
- Cigarette smoke
- Aerosols, perfumes, cleaning products, essential oil diffusers
- Emotions
- Exercise

Should We Get Rid of the Dog????

Recommendation 5: In individuals with asthma who do not have sensitization to specific indoor allergens or who do not have symptoms related to exposure to specific indoor allergens, the Expert Panel conditionally recommends against allergen mitigation interventions as part of routine asthma management.

Conditional recommendation, low certainty of evidence

Recommendation 6: In individuals with asthma who have symptoms related to exposure to specific indoor allergens, confirmed by history taking or allergy testing, the Expert Panel conditionally recommends a multicomponent allergen-specific mitigation intervention.

Conditional recommendation, low certainty of evidence

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Definitions

- phe·no·type
  - the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment
- end·o·type
  - a subtype of a condition, which is defined by a distinct functional or pathobiological mechanism
- gen·o·type
  - the genetic constitution of an individual organism

Phenotypes

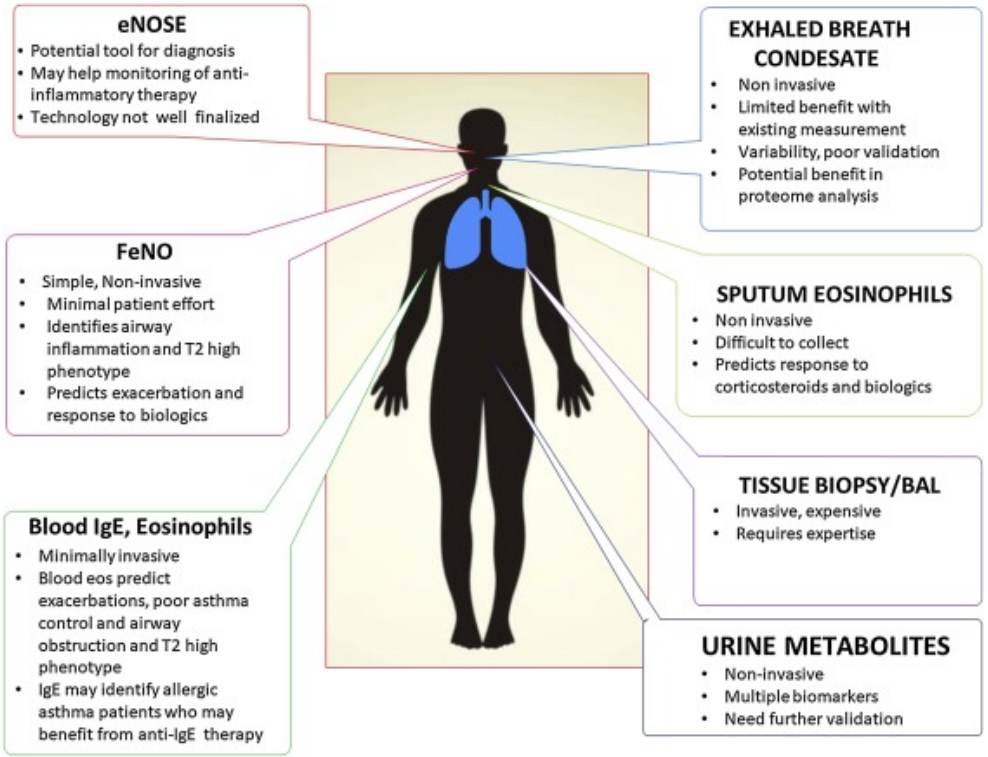
- 59% - never/infrequent
- 16% - transient early
- 16% - late onset
- 9% - prolonged early
- 7% - persistent
- 3% - intermediate

Endotypes

- Aspirin sensitive asthma
- Allergic bronchopulmonary mycosis
- Allergic asthma
- Asthma predictive index positive asthma
- Late onset adult asthma
- Cross country skier asthma

Clin Rev Allergy Immunol. 2019 Apr;56(2):219-233.

The Future is Now: Biomarkers



Semin Immunol. 2019 Dec;46:101332.

Exhaled Nitric Oxide

Recommendation 1: In individuals ages 5 years and older for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed, the Expert Panel conditionally recommends the addition of FeNO measurement as an adjunct to the evaluation process.

Conditional recommendation, moderate certainty of evidence

Recommendation 3: In individuals aged 5 years and older with asthma, the Expert Panel recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity. FeNO should only be used as part of an ongoing monitoring and management strategy.

Strong recommendation, low certainty of evidence

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Goals of Asthma Therapy

- Reduce chronic symptoms
- Prevent exacerbations
- No activity restrictions
- Prevent ER visits/hospitalizations
- Minimize adverse effects of treatment

Asthma Management

- 4 components of care:
  - Assessment and monitoring
  - Education for a partnership in care
    - Family understanding and ownership of their disease is crucial to improving outcomes
  - ***Control of environmental factors and co-morbid conditions that affect asthma***
  - Medications

Figure I.b: Stepwise Approach for Management of Asthma in Individuals Ages 0–4 Years

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 0–4 Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6**
Preferred	PRN SABA and At the start of RTI: Add short course daily ICS▲	Daily low-dose ICS and PRN SABA	Daily medium-dose ICS and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily montelukast* or Cromolyn,* and PRN SABA		Daily medium-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA

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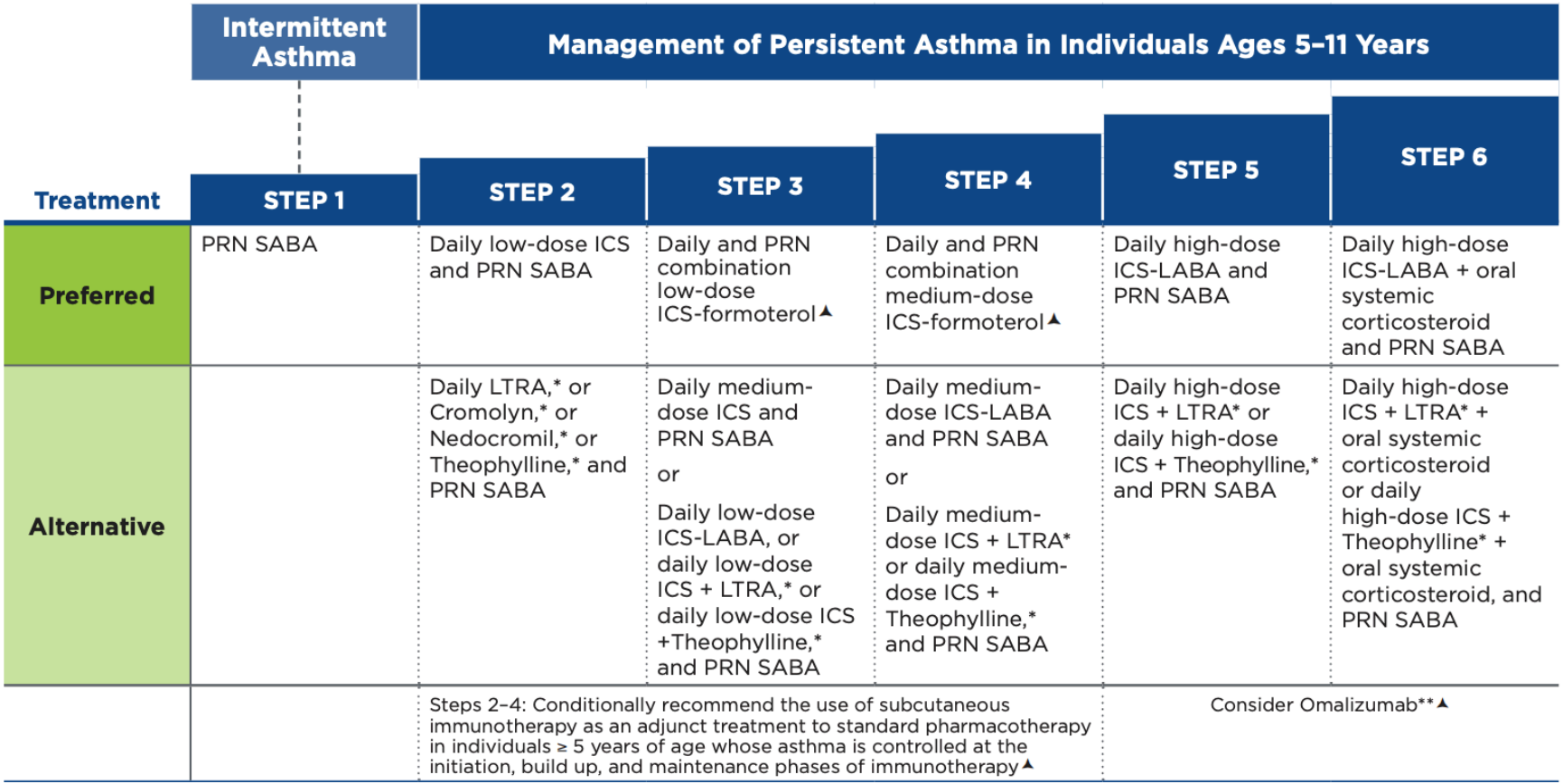
Figure I.c: Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years



Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
	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**▲	

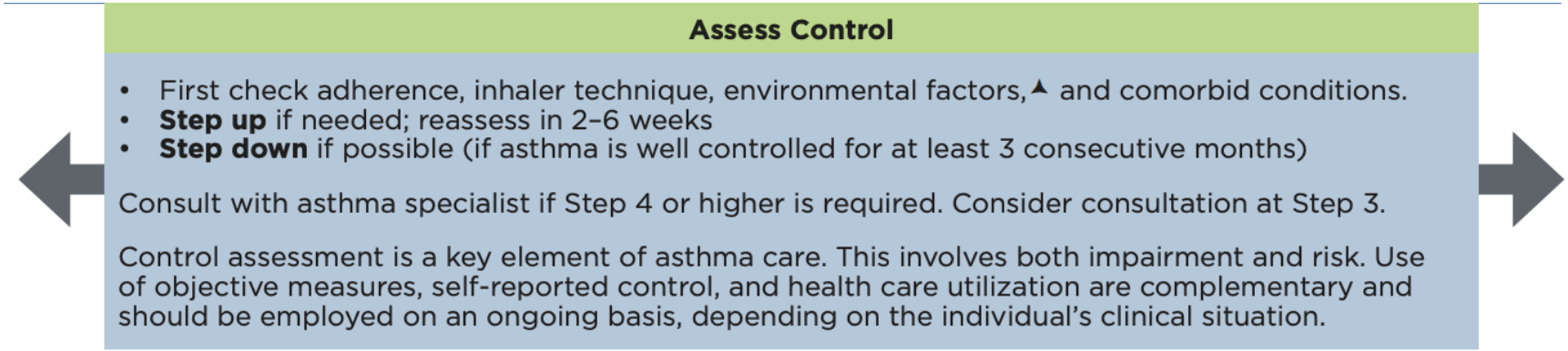
https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	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	
		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 adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

The MOST Important Part of Stepwise Therapy



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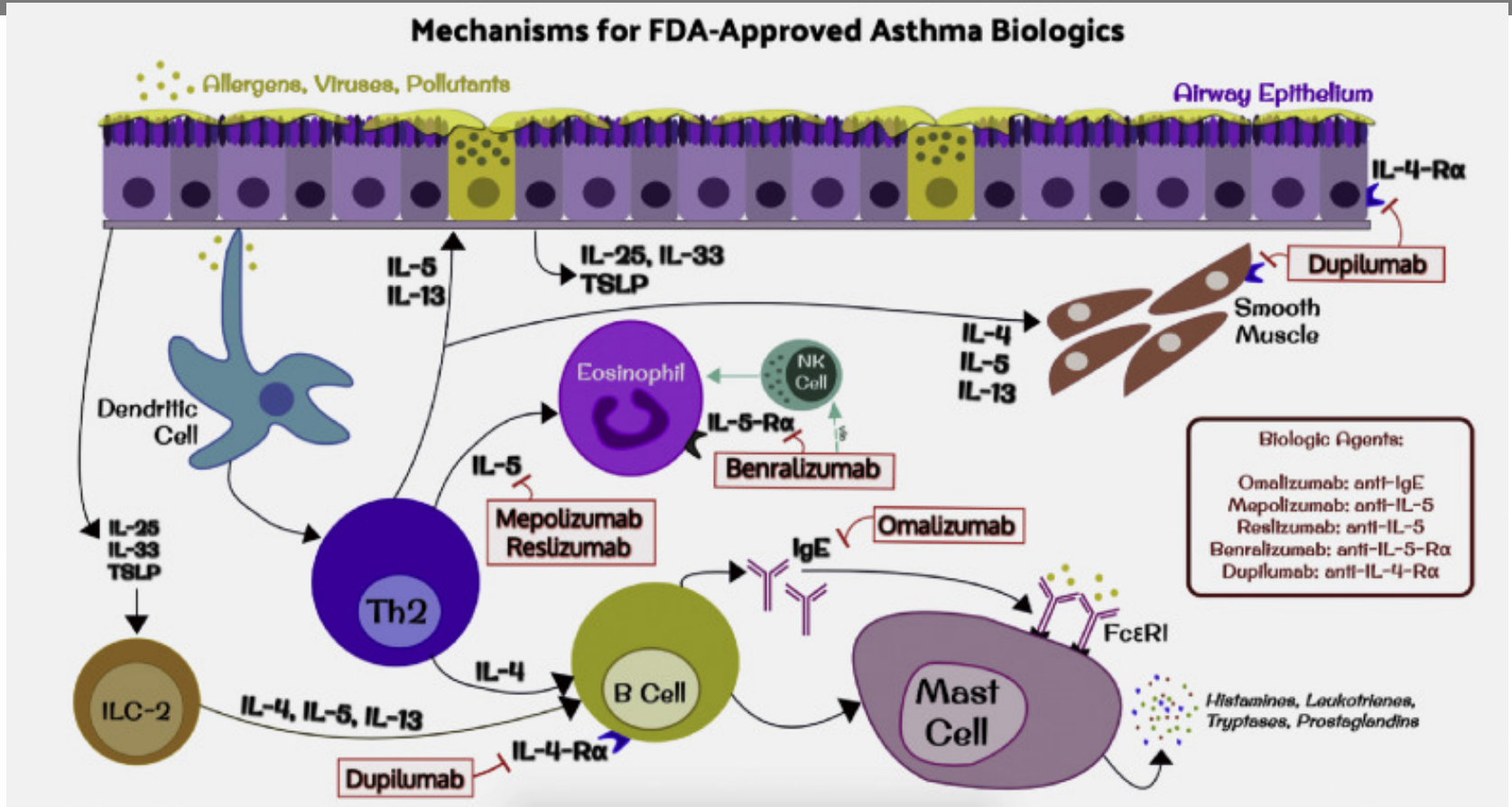

Doroudchi A, et al. Ann Allergy Asthma Immunol. 2020;124(1):44-56.

Cost…Biomarkers…Patient Selection

Key Messages

- Biologic therapy for asthma is not considered cost-effective based on current pricing structures.
- Manufacturers must seriously consider price reduction to provide fair value for biologic therapy.
- Practitioners should direct therapy only to responders to improve cost-effectiveness, including using biomarkers before initiating treatment and monitoring for response to treatment.
- A recent publication by the Global Initiative for Asthma provides an algorithmic approach to identifying adolescent and adult patients who can be considered candidates for biologic therapy.
- A recent Institute for Clinical and Economic Review report provides detailed information on available cost-effectiveness data and what is needed to improve cost-effectiveness of these treatments.
- Direct head-to-head studies of biologics are needed to adequately assess their comparative effectiveness.

Anderson WC, Szefler SJ. Ann Allergy Asthma Immunol. 2019;122(4):367-372

Individualized Use of ICS

Recommendation 9: In children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, the Expert Panel conditionally recommends starting a short course of daily ICS at the onset of a respiratory tract infection with as-needed SABA for quick-relief therapy compared to as-needed SABA for quick-relief therapy only.

Conditional recommendation, high certainty of evidence

Recommendation 10: In individuals ages 12 years and older with mild persistent asthma, the Expert Panel conditionally recommends either daily low-dose ICS and as-needed SABA for quick-relief therapy or as-needed ICS and SABA used concomitantly.

Conditional recommendation, moderate certainty of evidence

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Individualized Use of ICS

Recommendation 12: In individuals ages 4 years and older with moderate to severe persistent asthma, the Expert Panel recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.

Strong recommendation, high certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4–11 years

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We Can All Be SMART About ICS/LABAs

Recommendation 12: In individuals ages 4 years and older with moderate to severe persistent asthma, the Expert Panel recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.

Strong recommendation, high certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4–11 years

Recommendation 13: In individuals ages 12 years and older with moderate to severe persistent asthma, the Expert Panel conditionally recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.

Conditional recommendation, high certainty of evidence

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

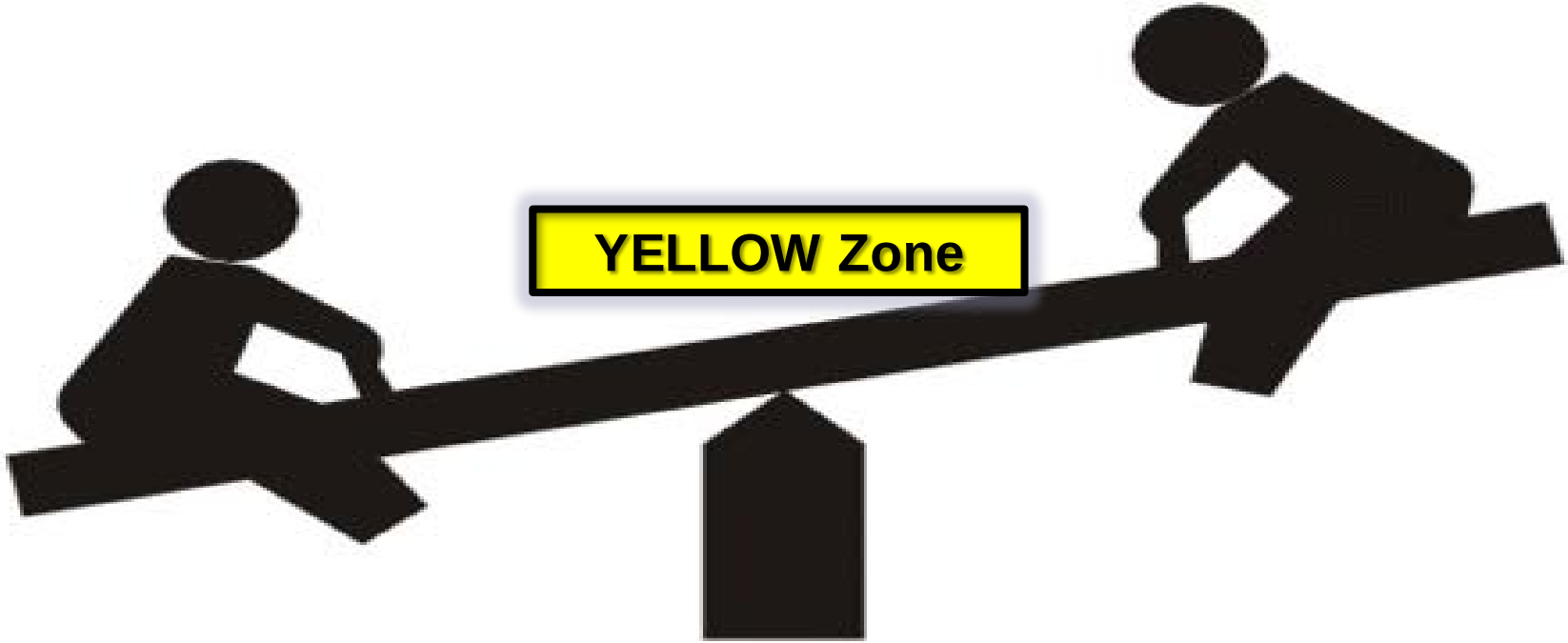
Asthma Action Plans

- Asthma action plans typically follow a “traffic light” model
  - **Green** – daily management when symptoms are well controlled
  - **YELLOW** – FOREWARNS ACUTE LOSS OF CONTROL AND IMPENDING EXACERBATION
  - **Red** – onset of severe exacerbation requiring course of systemic corticosteroids and contact with health care provider

- *Every* patient should be provided with an asthma action plan
- Include instructions for recognition of loss of control AND activation of the yellow zone intervention plan

GREEN Zone → All systems clear

RED Zone → Too late, seek care



Self-Management

- Instruct patients to activate the yellow zone intervention plan when there is acute loss of asthma control in a setting outside a medical care facility, i.e. home

- Yellow zone is defined as:
  - An increase in asthma symptoms
  - An increase in use of reliever medications
  - A peak flow rate decrease of at least 15% or lower than 80% of personal best
  - The presence or increase in nocturnal asthma symptoms

*Need to consider patient variability in baseline symptoms

Management of acute loss of asthma control in the yellow zone: a practice parameter. Ann Allergy Asthma Immunol. 2014 Aug;113(2):143-59.

What if Yellow Zone is Started Too Early?

- A **“false”** start may lead to initiation of management when not necessary

BUT…

- Risk of a **“late”** start may result in episode progression and need for systemic corticosteroids/ER care

Don’t want to be late!

Before We Go Any Further…

- Please
- **Please**
- ***I beg of you***

- Do not teach patients that albuterol is an ‘emergency’ inhaler

- Educate patients/parents that albuterol is a ‘rescue’ or ‘reliever’ inhaler
  - If you have asthma, you will need albuterol
- When parents are taught ‘emergency use only’
  - Removes empowerment for self management
  - Delayed administration
  - Rush to the ER

Albuterol Use

- 2007 NHLBI Guidelines
  - *2-6 puffs of SABA every 3-4 hours* for 24-48 hours for home use

- 2018 Global Strategy for Asthma Management and Prevention
  - **4-10 puffs of SABA every 20 min for 1 hour**
  - 4-10 puffs of SABA every 3-4 hours with good response

MDI vs. Nebulizer

- For mild-to-moderate exacerbation (yellow zone)
- Cochrane Review in 2013
  - 1897 children, 729 adults in 39 trials mainly ED setting
- Use of MDI with spacer equivalent to nebulizer
    - Various markers of clinical outcomes
- Nebulizers associated with more adverse events
    - Tachycardia
    - Tremor
    - Longer LOS

J Pediatr Pharmacol Ther. 2004 Oct;9(4):226-34.

Additional Considerations

- Macrolides
- At home oral corticosteroid prescriptions
- Long acting muscarinic therapy

Recommendation 16: In individuals ages 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA.

Conditional recommendation, moderate certainty of evidence

https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

Conclusions

- Proper diagnosis of asthma can aid management and improve control
- Treatment requires much more than just medication
- Utilize knowledge of asthma phenotypes and biomarkers to guide therapy
- Use of ICS/LABAs can be very effective and highly individualized