Differential Diagnosis of Severe Asthma in Children

Kenan Haver, MD

Division of Pulmonary Medicine

Boston Children's Hospital

Boston Children's

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosure of Potential Conflict of Interest

I have the following relations to disclose:

Entity: UpToDate Role: Author Received: Royalty

Objectives

- Define severe asthma
- Recognize factors that may impact asthma control
- Consider a differential diagnosis for asthma symptoms in children

Pediatric Asthma is the Most Common Chronic Respiratory Disease in the Developed World

- The highest prevalence found in the US, the UK and Australia [1]
  - The increasing prevalence previously reported appears to have plateaued or even declined

- In resource poor countries, asthma prevalence is generally increasing [2] and both severity and mortality are higher [3, 4]

1. Asher MI, et al. ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368:733-743
2. CHEST 2006; 130:4S–12S
3. Lancet 2006; 368: 733–43
4. WHO mortality database 2014 update

Asthma in Children in the US

- 4.7 million children (6.5%) currently have asthma
  - 12.3 % of African American children and 5.5 % of white children in the United States [1]
- The majority of children with asthma have mild or moderate disease
  - Small proportion (2-5%) have severe asthma
- Almost half (43%) have at least one exacerbation per year

1. Pediatric Annals • Vol. 48, No. 3, 2019
2. www.cdc.gov/asthma/most_recent_national_asthma_data.htm

Asthma in Children

- Asthma exacerbations are the number one reason for admission to children's hospitals outside the neonatal period

- Mortality from asthma, although decreasing, still occurs.
  - **145** in US (most recent data from CDC)

- Asthma care costs in the US are estimated to be $50 billion per year

1. Pediatric Annals • Vol. 48, No. 3, 2019
2. ATS press release

Asthma

- The diagnosis of asthma in children is clinical. It is based on recognising a characteristic pattern of episodic symptoms in the absence of an alternative explanation.

- Symptoms are caused by inflammation resulting in narrowing of small airways and may include:
  - wheezing
  - cough
  - difficulty breathing
  - chest tightness

- Supporting evidence includes a family history of atopy, parental asthma, a personal history of eczema, seasonal rhinitis, or food allergy.

- Response to albuterol or a short course of oral steroids is suggestive of asthma.

Pediatr Ann. 2019;48(3):e103–e109.

Severe Asthma in Children:

2007 NHLBI Guidelines for the Diagnosis and Treatment of Asthma

- Asthma severity is the intrinsic intensity of the disease process

- Based on the most severe impairment or risk category in which any feature occurs
  - Impairment domain assessed by patient's recall of previous 2–4 weeks and/or by spirometry

2007 NHLBI Guidelines for the Diagnosis and Treatment of Asthma Expert Panel Report 3

Case Study:
9-Year-Old Boy with Asthma

- Coughs every day
- His mother hears him cough and wake up every night
- Uses albuterol at least twice per day and sometimes more often.
- He can no longer play soccer because he gets so out of breath.
- His FEV_1 was 58% and FEV_1/FVC was 74 before treatment with albuterol.

What is the severity of his asthma?

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	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	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%

- 9 year old boy with asthma coughs every day
- Coughs a wakes up every night
- Uses albuterol at least twice per day and sometimes more often.
- He can no longer play soccer because he gets so out of breath.
- His FEV_1 was 58% and FEV_1/FVC was 74 before treatment with albuterol.

www.nhlbi.nih.gov/files/docs/guidelines/asthgdln/pdf

What is the Severity of his Asthma?

The EPR 3 Guidelines on Asthma

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤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	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%

- Based on the most severe impairment category in which any feature occurs he has severe asthma

www.nhlbi.nih.gov/files/docs/guidelines/asthgdln/pdf

Determinants of Severe Asthma

- burden of symptoms
- frequency of the use of quick relief medication
- spirometry
- **the intensity of treatment required to maintain asthma control**

2020 FOCUSED UPDATES TO THE **Asthma Management Guidelines**

AGES 5–11 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

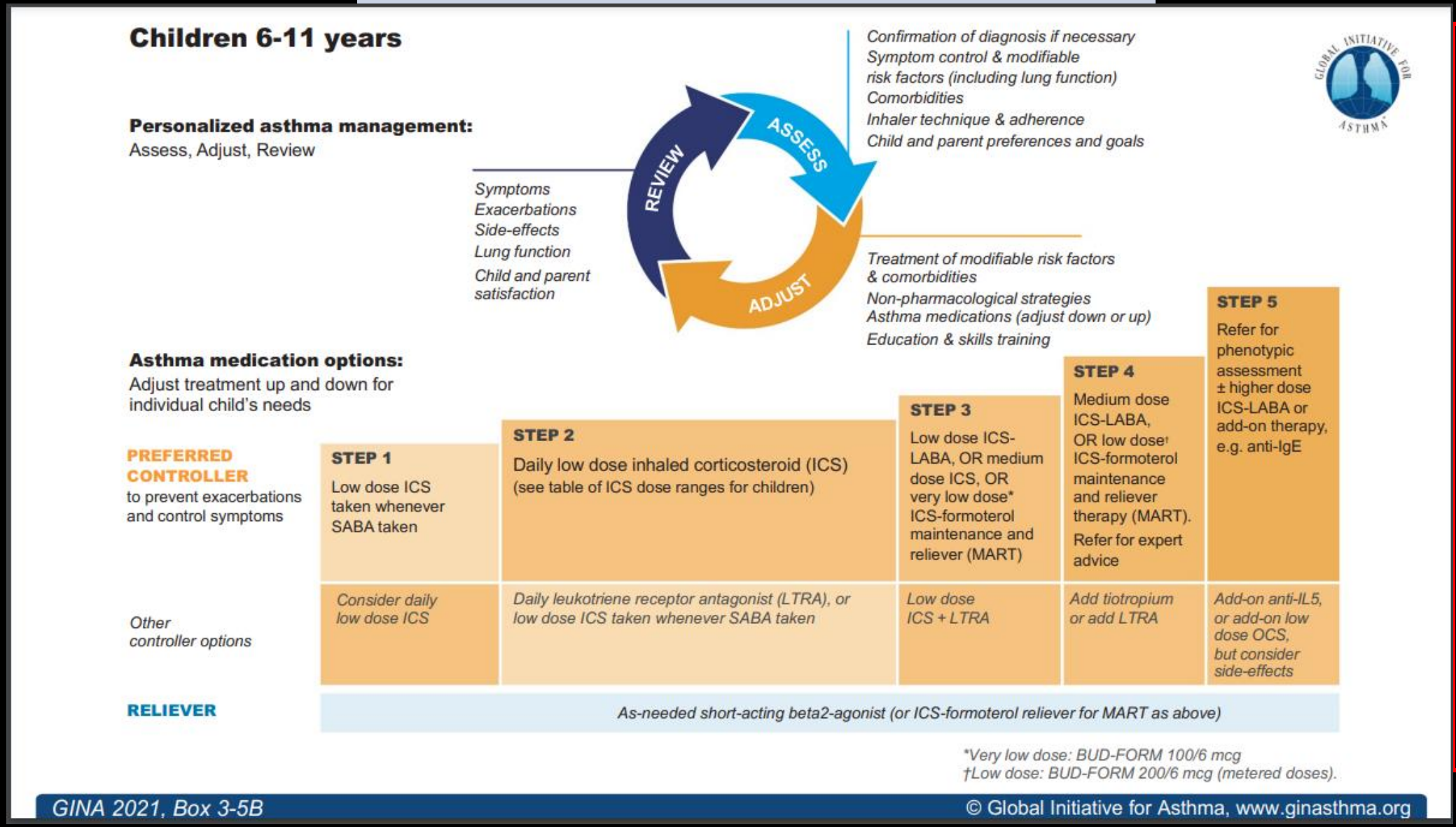
	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6**
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose 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**▲	

Steps 5-6 are severe

Journal of Allergy and Clinical Immunology 2020 1461217-1270DOI: (10.1016/j.jaci.2020.10.003)

GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

Updated 2021



-Severe asthma is asthma that **remains uncontrolled** despite optimized treatment with high dose ICS-LABA, or that **requires** high dose ICS-LABA to prevent it from becoming uncontrolled.

-Severity no longer references GINA steps.

https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

Severe Asthma in Children

- The majority of children with asthma have mild or moderate disease
- A small proportion, approximately 2-5%, are considered to have severe asthma
- Those with severe asthma have chronic symptoms or recurrent exacerbations despite maximum treatment

When asthma is not well controlled: Is it severe?

-paraphrasing Prof Andrew Bush and colleagues

The most important part of managing asthma in children is, and will remain for the foreseeable future, getting the basics right.

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

When asthma is not well controlled: Is it severe?

-model developed by Prof Andrew Bush and colleagues

- **Not asthma**
  - exclude an alternative diagnosis

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

Case 2: Acute onset of respiratory distress with wheezing

- 3 year old presented to the ED with cough and wheezing
- Seen by his pediatrician one week ago, diagnosed with a viral infection
- Returned with persistent cough, wheezing noted
- He was treated in the office with albuterol which was then prescribed for use at home
- No recent respiratory illness
- Family history of seasonal allergies but no asthma

Case 2: Acute onset of respiratory distress with wheezing

- In the ED he was in mild respiratory distress
- RR 42
- Oxygen saturation in RA 98%
- Exam: Stridor audible on auscultation with mild tracheal tugging and wheezing.
- He was treated with albuterol, combined with ipratropium, and dexamethasone.
- Wheezing did not improve

When asthma is not well controlled: Is it severe?

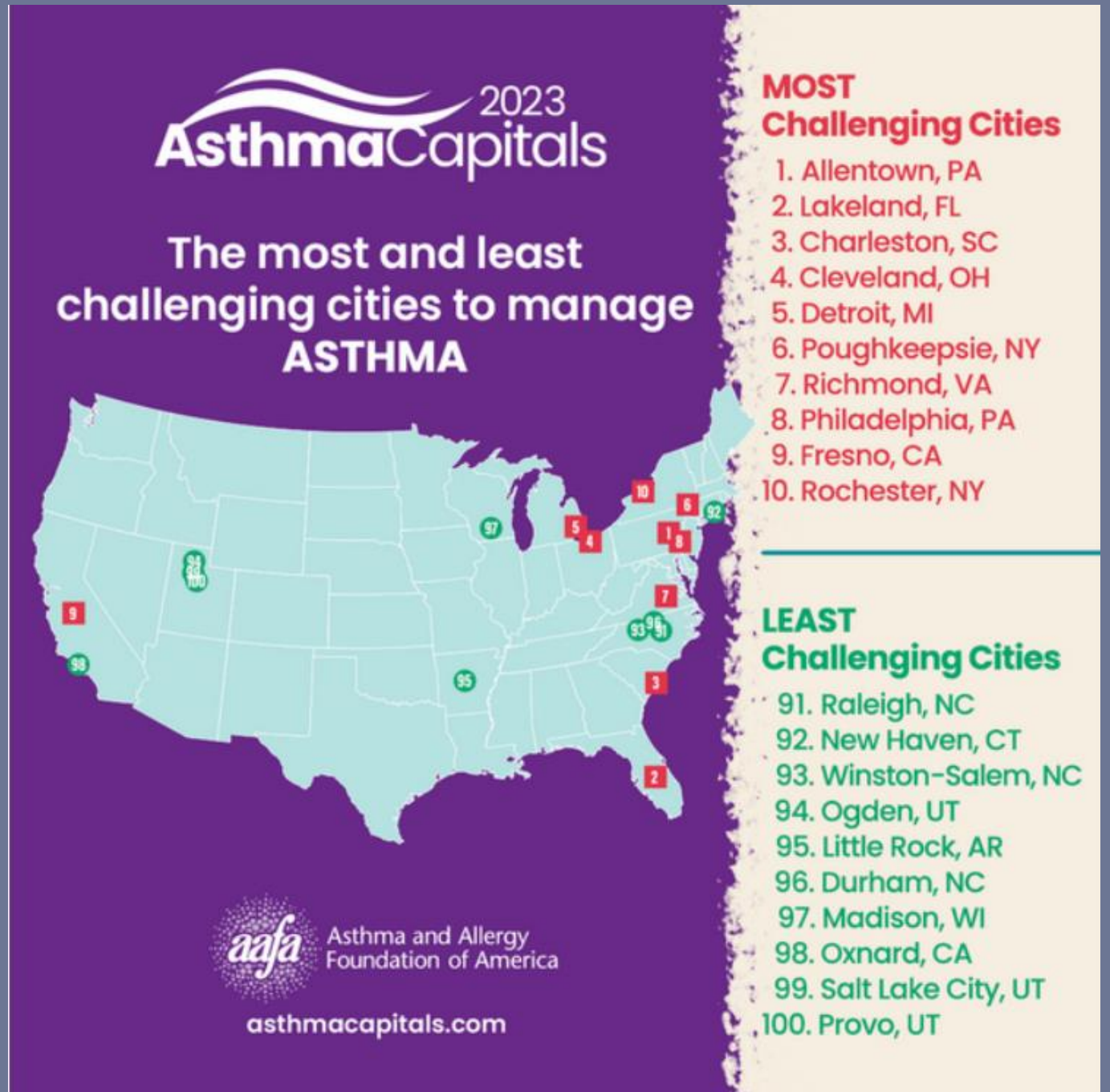
- Not asthma
  - exclude an alternative diagnosis
- Difficult asthma
  - improves when the basic management needs, such as adherence and inhaler technique, are corrected
  - if prescribed Flovent they have been able to find an alternative that is covered by their insurance
  - Ii Single Maintenance and Reliever Therapy (SMART) has been recommended they can find an inhaler that their insurance will cover
- Asthma plus
  - consider comorbidities

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

Common Comorbidities Associated with Severe Asthma

Rhinosinusitis	cough, upper-airway wheeze, and sputum production
Stress	the links between the airway and brain are complex and bidirectional
Food allergy	high prevalence of food allergy in children with asthma admitted to PICU
Obesity	shortness of breath with exercise, increased asthma severity, decreased response to steroids
COVID	decreased frequency of acute asthma episodes

Respirology (2017) **22**, 886–897

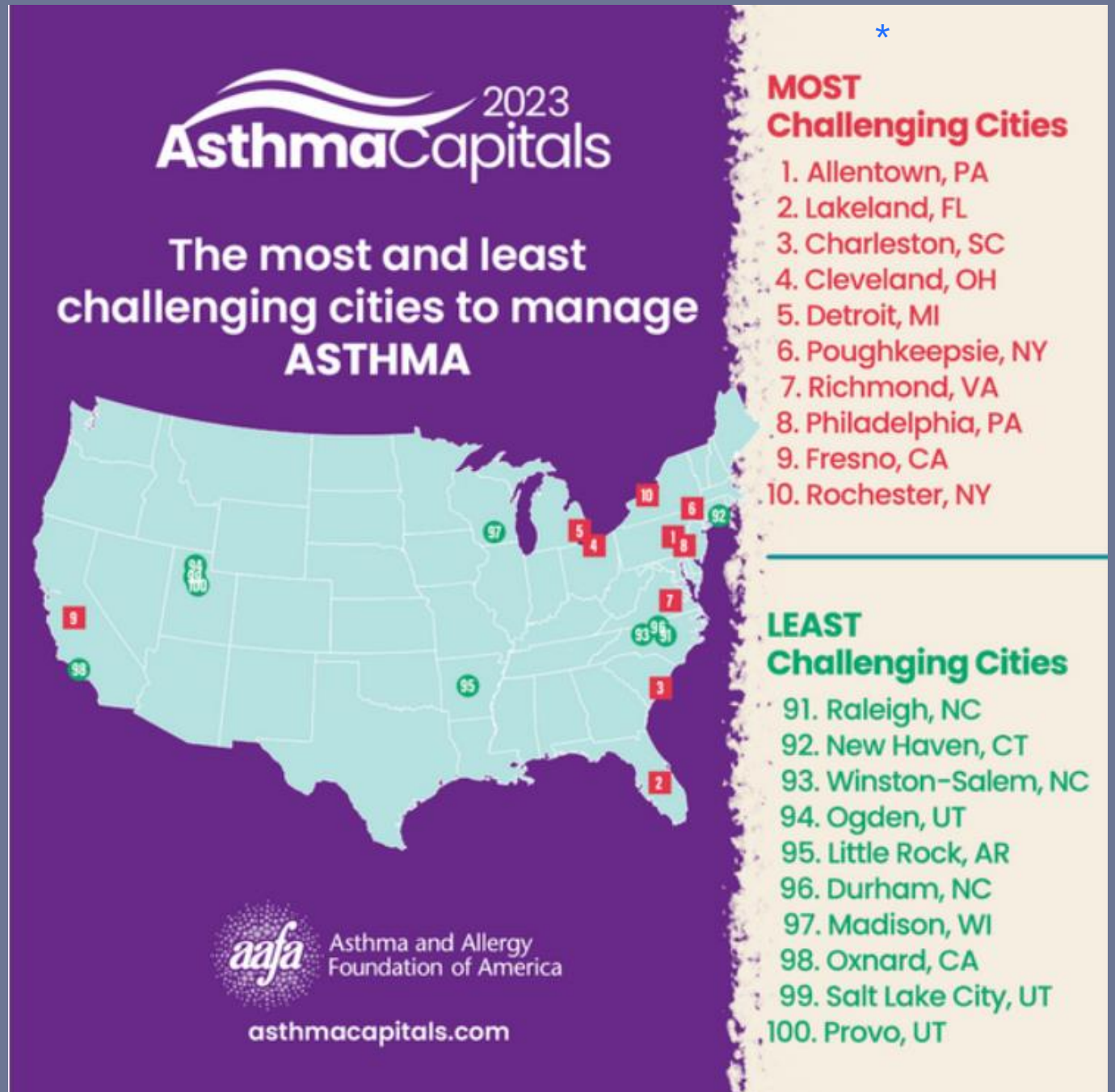


Asthma and Allergy Foundation of America Asthma Capitals™ Report

- ❑ Asthma prevalence
- ❑ Asthma-related emergency room visits
- ❑ Asthma-related deaths

"…air quality in Salt Lake City remains among the worst in the United States. "
Salt Lake City Air Quality Index (AQI) and Utah Air Pollution

https://aafa.org



*

What makes these cities the most challenging?

- Poverty
- Lack of health insurance
- Lack of access to asthma specialists
- Pollen counts
- Air pollution
- Smoking laws

Case 3: 14 year old young woman with an asthma exacerbation

- 14 year old young woman with a history of asthma and allergies presented to the ED with wheezing and shortness of breath.
- For the past 2 days she has been using albuterol every 2 hours with minimal relief.
- She did not come to the ED sooner because she did not want to be admitted to the hospital again.
- Fluticasone 110 mcg, montelukast, nasal fluticasone and cetirizine have been prescribed but she does not always remember to take them.
- On examination her RR was 28 bpm, RA oxygen saturation 94%, and she had diffuse bilateral inspiratory and expiratory wheezing.

Case 3: 14 year old young woman with an asthma exacerbation

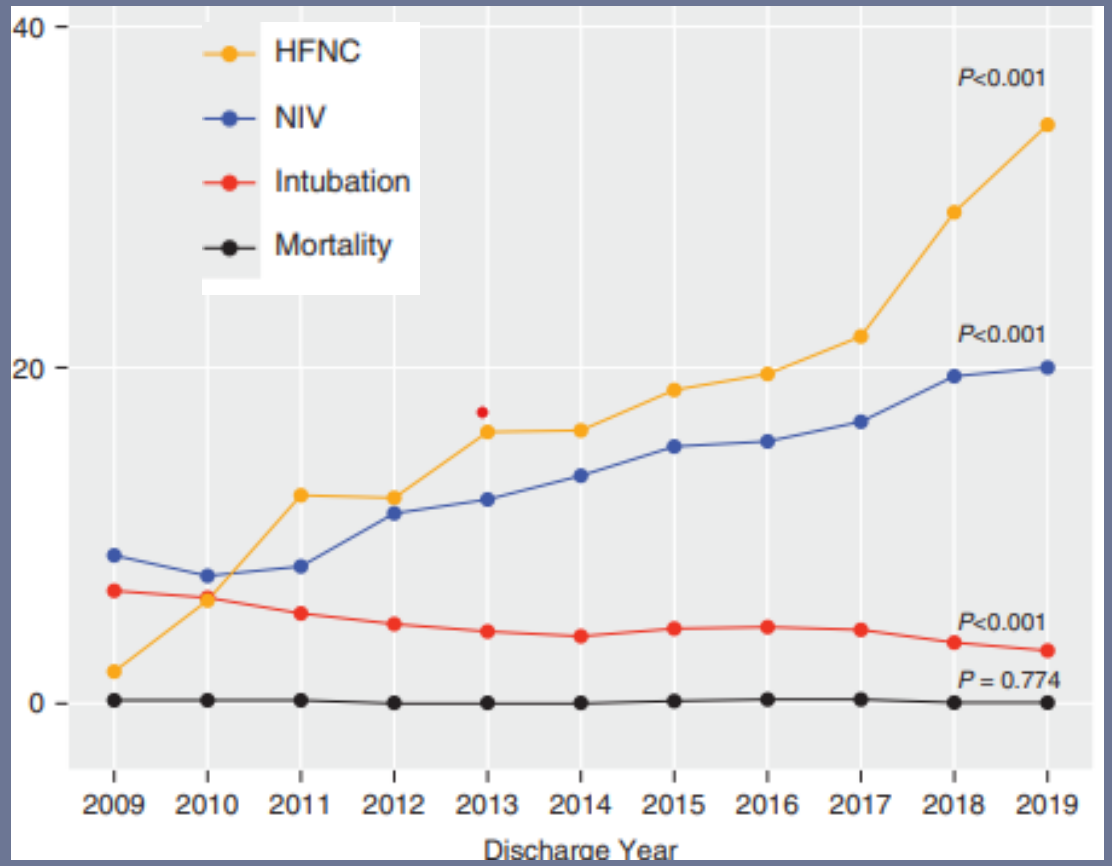
- In the ED she was treated with albuterol combined with ipratropium and dexamethasone
- When her dyspnea and wheezing persisted she was treated with magnesium and albuterol every 1 hour.
- She admitted to the intensive care unit where she received noninvasive ventilation

Noninvasive Ventilation (NIV) in Asthma

- NIV is used, together with conventional pharmacological treatment, to decrease the respiratory muscle work that is much increased during the episodes of acute bronchoconstriction
  - improves ventilation, decreases the sensation of dyspnea, and ultimately avoids the need for intubation and mechanical ventilation
- Rates of NIV are increasing while intubation rates are decreasing

European Respiratory Journal 2017 50: 1602426

Noninvasive Ventilation (NIV) in Asthma



- 67,614 admissions for 56,727 patients
  (Some admitted more than once)
- Intubation decreased from 6.9% to 3.4% ($p<0.001$) over time
- Noninvasive ventilation increased from 8.9% to 20% ($p<0.001$)
- No change in mortality

Smith, Dinh, Ly, et al. Ann Am Thorac Soc. 2023 Feb;20(2):245-253.

Noninvasive Ventilation (NIV) in Asthma

- NIV is used, together with conventional pharmacological treatment, to decrease the respiratory muscle work that is much increased during the episodes of acute bronchoconstriction
  - improves ventilation, decreases the sensation of dyspnea, and ultimately avoids the need for intubation and mechanical ventilation
- Rates of NIV are increasing while intubation rates are decreasing
- Patients >12 years were more likely to respond to NIV than younger patients
  - Patients ages 6- to 12-years had the highest odds of requiring intubation
- Black and other non-White patients were more likely to require NIV
- Obese patients were more likely to require NIV

Smith, Dinh, Ly, et al. Ann Am Thorac Soc. 2023 Feb;20(2):245-253.

Case 3: 14 year old young woman with an asthma exacerbation – additional history

- She improved and did not require intubation
- Anticipating discharge medication adherence and trigger avoidance were discussed

Case 4: 8 year old young man with asthma and persistent coughing

- 8 year old young man with asthma presented to the ED with a history of persistent coughing
- His asthma had previously been well controlled on treatment with fluticasone 44 mcg 2 puffs twice per day and rarely needed to use albuterol
  - He had been using a valved holding chamber
- For the past week he has been taking albuterol several times per day he has been waking up coughing.
- After using albuterol he coughs less but it has not resolved.

Case 4: 8 year old young man with asthma and persistent coughing

- His asthma had been under good control until last week when he was visiting his cousins over labor day weekend
- He has no known allergies
- His cousins do not have any pets
- His mother reports no ill contacts
- He does not recall any choking episodes
- In the ED he is coughing
  - RR 24 bpm
  - Oxygen saturation in RA 96%
  - On exam he has equal breath sounds with inspiratory and expiratory, bilateral wheezing

Most likely trigger?

Case 5: 14 year old Basketball Player with Shortness of Breath with Exercise

- Diagnosed with exercise induced asthma at age 7 years
- Since the start of the basketball season she reports feeling short of breath during strenuous practices and games
- She frequently stops playing after fast breaks but does not signal her coach to take her off the court

Case 5: 14 year old Basketball Player with Shortness of Breath with Exercise

- She was seen by her family practitioner
  - Her chest was clear
  - Oxygen saturation in room air was 97%

➢She was given instructed to use an additional inhalation of budesonide/formoterol before each practice and each game

  - She was able to practice with less shortness of breath
  - She still had to stop during gamers

Shortness of Breath with Exercise

- Instructed to use additional puffs of albuterol when she became short of breath
- Started on a combination of an inhaled steroid and long acting beta agonist
- Still could not play more than several minutes
- Referred to the pulmonary clinic for further evaluation

Pediatric Pulmonary Clinic

- Chest was clear
- Oxygen saturation in room air 97%
- Spirometry: No obstructive defect
- Exercise study
  - 20% drop in FEV_1
  - Reversed following treatment with albuterol

Differential Diagnosis of Severe Asthma in Children[1]

- Not asthma
  - exclude an alternative diagnosis

- Difficult asthma
  - improves when the basic management needs, such as adherence and inhaler technique, are corrected

- Asthma plus
  - consider comorbidities

- Therapy resistant
  -if uncontrolled despite optimized treatment it is time to step-up care

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.