CHILDREN BREATHING EASIER, FAMILIES LIVING BETTER: THE EXPANDED USE OF BIOLOGICS TO TREAT PEDIATRIC ASTHMA

Terri G. Magruder, MD, MPH
Nov. 12, 2020
Alabama Dept. of Public Health
UAB Pediatric Pulmonary Center

DEFINING ASTHMA

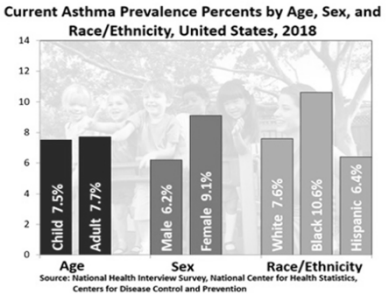
- Asthma is a chronic inflammatory disorder of the airways characterized by variable and recurring symptoms caused by:
  1. Bronchial hyperresponsiveness
  2. Airflow obstruction
  3. Bronchial edema due to inflammation

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, National Heart Lung and Blood Institute, U.S. Department of Health and Human Services, 2007.

SIGNS AND SYMPTOMS OF ASTHMA

Recurrent or Episodic Symptoms of:
1. Wheezing
2. Nocturnal or Frequent Daytime Cough
3. Chest Tightness
4. Shortness of Breath

These symptoms often are worse or occur with exercise, viral infections, weather changes, allergen or environmental irritant exposure, strong emotions, and stress



Centers for Disease Control and Prevention https://www.cdc.gov/asthma/asthmadata.htm accessed Nov. 7, 2020

PEDIATRIC ASTHMA IN THE U.S.

ED visits: 625,000 in 2017[1]

Hospitalizations: 76,000 in 2017[1]

CDC National Asthma Control Program 2012-14: 50.3% of children with asthma had uncontrolled asthma[1]

13.8 million missed school days in 2013[1]

50% of asthma health care costs are related to uncontrolled asthma[2]

1. Centers for Disease Control and Prevention : https://www.cdc.gov/asthma/healthcare-use/2017/data.htm , https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-children.htm, https://www.cdc.gov/asthma/asthma_stats/missing_days.htm, https://www.cdc.gov/asthma/healthcare-use/2017/data.htm, Accessed Nov. 7, 2020
2. Yaghoubi, Mohsen, et al. "The Projected Economic and Health Burden of Uncontrolled Asthma in the United States." *Am J Respiratory Crit Care Med.*, vol. 200, no. 9, Nov. 2019, pp. 1102–12, doi:10.1164/rccm.201901-0016OC.

ASTHMA SEVERITY CLASSIFICATIONS

Mild intermittent

Mild persistent

Moderate persistent

Severe persistent

Treatment is directed based on initial disease severity at diagnosis and then adjusted based on symptoms and exacerbation control over time

WHAT CAUSES PEDIATRIC ASTHMA?

It is the interaction between host factors and environmental exposures that triggers a certain immune response that results in the asthma phenotype

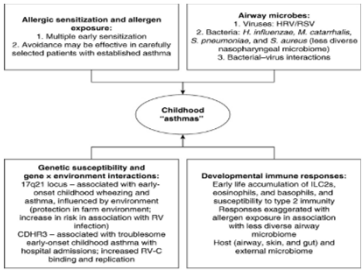
Key Factors:

Allergic sensitization and allergen exposure

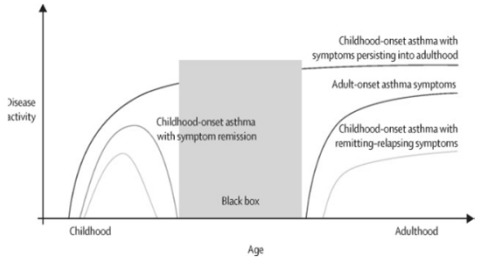
Airway Microbes

Genetic susceptibility

Developmental immune responses



Saglani S, Custovic A. Childhood Asthma: Advances Using Machine Learning and Mechanistic Studies. *Am J Respir Crit Care Med*. 2019;199(4):414–422. doi:10.1164/rccm.201810-1956CI



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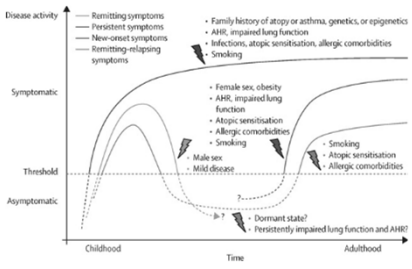


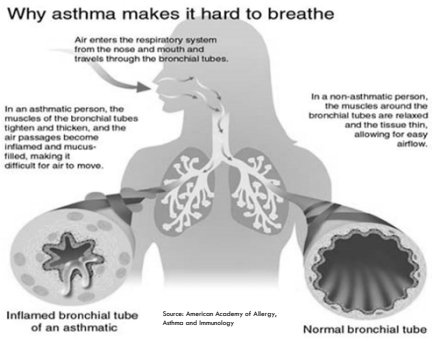
Lancet Respir Med. 2017 Mar;5(3):224-234. doi: 10.1016/S2213-2600(16)30187-4. Epub 2016 Sep 22

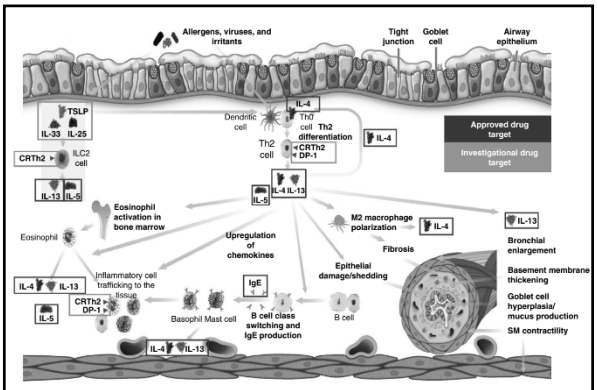
IMMUNOLOGY OF ASTHMA

Resembles a complex syndrome rather than a single disease

Recognizing that asthma consists of multiple phenotypes with a variety of pathophysiologic mechanisms or endotypes

Endotypes are disease subtypes characterized by distinct pathophysiological mechanisms





McGregor MC, Kings JG, Nair P, Castro Mam. Role of Biologics in Asthma. J Respir Crit Care Med. 2019 Feb 15;199(4):433-445.

ASTHMA CLASSIFICATIONS

T2-High
- Approximately ½ patients with asthma
- Activates IL-4, IL-5, and IL-13
- Encompasses both allergic and non-allergic eosinophilic asthma
- Allergic: IgE mediated
- Recruitment of mast cells, basophils, eosinophils

T2-Low
- Neutrophilic, mixed, or paucigranulocytic
- Poorly understood pathophysiology
- Less responsive to corticosteroids, fewer allergic symptoms, and often older at time of diagnosis

REDUCING IMPAIRMENT

Preventing symptoms

Minimizing quick relief medicine (bronchodilators) use to less than 2 days per week

Maintaining near normal pulmonary function

Maintaining normal activity levels

REDUCING RISKS

Preventing recurrent exacerbations
- ED visits, school absence, hospitalizations

Identifying triggers and environmental exposures

Prevent loss of lung function

Optimal Pharmacotherapy with minimal side effects

WELL-CONTROLLED ASTHMA MEANS:

Symptom-free days most of the time and not using quick-relief medicine more than two times a week

Sleeping through the night

Not missing school because of asthma

Able to exercise and play like other children

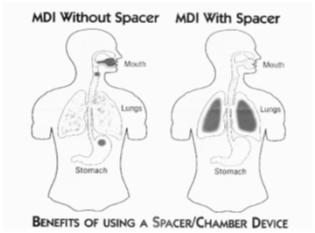
Fewer asthma flares and doctor visits

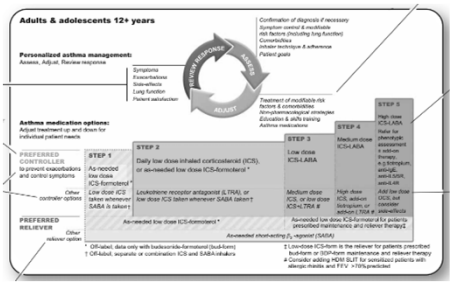
Fewer hospitalizations for asthma

ASTHMA MEDICATIONS

- Two Main Types: Quick Relief and Controller
- Quick Relief: Bronchodilators that relax smooth airway muscles to improve work of breathing and quickly decrease symptoms
  - Albuterol sulfate, Levalbuterol, Ipratropium Bromide
- Controller: Focused on decreasing inflammation in the airway to decrease edema and reduce bronchial hypersensitivity
  - Inhaled corticosteroids (ICS)
  - ICS/long acting beta agonists
  - Leukotriene receptor antagonists
  - Long acting anti-muscarinics

SPACERS





Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. Eur Respir J 2019; 53: 1901046 [https://doi.org/10.1183/13993003.01046-2019].

CHALLENGES TO PEDIATRIC ASTHMA TREATMENT

Large heterogeneous population

Acute and chronic disease populations differ

Limited access to self management disease education

Social disparities
- Substandard housing and poverty
- Missed work and school days
- Limited access to health care

Costs and Device Use

Non-adherence vs. lack of clinical response

IMPROVING ASTHMA MANAGEMENT

- Foster a good patient/clinician relationships
- Classify initial asthma severity
  - Medication therapy dictated by asthma severity
- Identify triggers and precipitating events
- Address comorbid conditions
- Develop an asthma action plan
- Assess disease self management knowledge

WHEN TO SEE AN ASTHMA SPECIALIST

Poorly controlled asthma

History of 2 or more hospitalizations in the past 12 months

History of life threatening asthma exacerbation

Symptoms concerning for a comorbid condition that needs further evaluation

Requires targeted self management education

COMORBID CONDITIONS AND DIFFERENTIAL DIAGNOSES TO CONSIDER

Allergic Rhinitis
Aspiration
Atopic Dermatitis
Bronchitis
Cystic Fibrosis
Depression or Anxiety
Eosinophilic Esophagitis
Eosinophilic Pneumonia
Food Allergies
Gastroesophageal Reflux Disease
Habit Cough
Immune Disorders
Obesity
Obstructive Sleep Apnea
Tracheomalacia
Vascular Rings
Vocal cord dysfunction

DEFINING SEVERE ASTHMA

Asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy”.

Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.

SEVERE ASTHMA

Estimated to be 5-10% of patient that remain poorly controlled despite adherence to standard treatment

Carry much of the morbidity, mortality, and healthcare utilization of the disease

Difficult to treat vs. difficult to control

BIOLOGICS ASSESSMENT FOR MODERATE TO SEVERE ASTHMA

Optimize medication management and adherence with documented assessment of adherence

Evaluation for comorbid conditions complete

Allergy screening: Skin testing, Environmental RAST and CBC

Patients with food allergy history should have formal allergy evaluation

Economically responsible

NEW HOPE FOR SEVERE ASTHMA

Biologics that target specific inflammatory modulators that have been identified to play a key role in the pathogenesis of T2-high asthma

Omalizumab (Xolair®) IgE

Mepolizumab (Nucala®)- IL-5

Benralizumab (Fasenra®)-IL-5

Dupilumab (Dupixent®)-IL-4 and IL-13

**Reslizumab

OMALIZUMAB (XOLAIR®)

First biologic approved for asthma- IgE mediated asthma

IgE is produced by B-cells in response to allergen activation of cell mediated immune response

Prevents IgE from binding to its high affinity receptor on mast cells and basophils, which decreases the release of proinflammatory mediators and blunts the downstream allergic response

Approved ≥6yo and older, allergy to at least 1 perennial aeroallergen

Dosed Subcutaneous every 2-4 weeks based on total IgE level and weight

Given in office (0.1-0.2% risk of anaphylaxis)

XOLAIR® EFFICACY AND LONGTERM CONSIDERATIONS

25% reduction in exacerbations

Minimal or equivocal improvement on lung function

Inconsistent affect on oral steroid dosing, but often can reduce ICS dosing

Shown some benefit in T2 Low asthma as well

Also approved for chronic urticaria

McGregor MC, Kings JG, Nair P, Castro Mam. Role of Biologics in Asthma. J Respir Crit Care Med. 2019 Feb 15;199(4):433-445.

MEPOLIZUMAB (NUCALA®)

Severe persistent asthma with eosinophilic phenotype

IL-5 is the primary cytokine involved in the recruitment, activation, and survival of eosinophils

Anti-IL-5: prevent IL-5 from binding to it's receptor on eosinophils reducing downstream eosinophilic asthma

Approved ≥6yo and ≥150 peripheral eosinophil count

Standard dosing s.c. injection: 40mg or 100mg q4 weeks

Now approved with autoinjector to allow home use

NUCALA® EFFICACY AND LONGTERM CONSIDERATIONS

50% reduction in exacerbations

Variable lung function

50% reduction in oral steroid dosing

Hypersensitivity reactions and increased risk for herpes zoster

- Confirm vaccination

Also approved for Eosinophilic granulomatosis with Polyangitis and Hypereosinophilic Syndrome

McGregor MC, Kings JG, Nair P, Castro Mam. Role of Biologics in Asthma. J Respir Crit Care Med. 2019 Feb 15;199(4):433-445.

BENRALIZUMAB (FASENRA®)

Severe persistent eosinophilia asthma

Anti-IL-5: blocks receptor on eosinophils and basophils preventing IL-5 from binding and subsequent recruitment and activation of eosinophils. It also attract natural killer cells to eosinophils to direct apoptosis (cell death)

Approved ≥12yo and ≥150 peripheral eosinophilia (greater effect if >300)

30mg s.c. q 4 weeks x3, and then q 8 weeks

Administered in office or at home with autoinjector

FASENRA® (BENRALIZUMAB) EFFICACY AND LONGTERM CONSIDERATIONS

60% reduction in exacerbations

Improved lung function

75% reduction in oral steroid dosing

Anaphylaxis/Hypersensitivity/ Headache/ Pharyngitis

McGregor MC, Kings JG, Nair P, Castro Mam. Role of Biologics in Asthma. J Respir Crit Care Med. 2019 Feb 15;199(4):433-445.

DUPILUMAB (DUPIXENT®)

Moderate to severe persistent asthma with eosinophilic phenotype or oral steroid dependent patients

Antibody binds IL-4$^{\alpha}$ receptor and blocks signaling of both IL-4 and Il-13 key cytokines that promote production of IgE and recruitment of inflammatory cells and stimulate goblet cell hyperplasia leading to airway hyperresponsiveness and airway remodeling

Approved ≥12yo and (≥150 peripheral eosinophil count)****

Loading dose 400mg or 600mg, then 200 or 300mg s.c. injection q2 weeks

Approved for home use (prefilled syringe or autoinjector)

DUPIXENT® EFFICACY AND LONG TERM CONSIDERATIONS

60% reduction in exacerbations

Improved lung function

70% reduction in oral steroid dosing

Injection site reaction and transient blood eosinophilia, keratitis

Also approved for atopic dermatitis (≥6yo) and chronic rhinosinusitis with nasal polyposis (≥18 yo)

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CHOOSING THE RIGHT BIOLOGIC

Head to head trials comparing the currently approved biologics do not exist

Biomarkers for asthma are not consistently available to identify

IL-5 modulators are of benefit in eosinophilic asthma

IgE modulator target allergic asthma

IL4 and IL-13 modulators target eosinophilia but with allergic cross over

SUMMARY

Asthma is a very common and complex disease associated with significant morbidity and mortality

Management requires a coordinated diagnostic and chronic disease management approach

Identification of asthma endotypes may further help us personalize treatment and predict clinical response

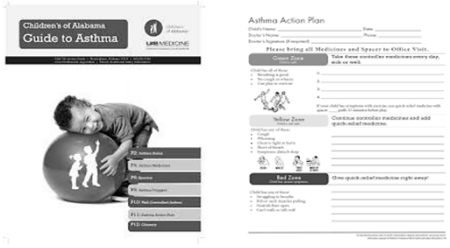
Biologics offer an expanded opportunity to treat severe asthma and improve family and patient quality of life

Further comparison research trials needed for biologics

"There is no alternative to establishing a therapeutic partnership between practitioners and patients in which needs, expectations, and obstacles patients face are included in the clinical decision making."

– Fernando D. Martinez, M.D.
Deputy editor, AJRCCM
Asthma and Airway Disease Research Center, University of Arizona

ASTHMA EDUCATION RESOURCES



www.childrensal.org/asthma