

# Difficult-to-Treat and Severe Asthma

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7/29/22



# Objectives

1

Define difficult-to-treat and severe asthma

2

Discuss epidemiology and pathophysiology of asthma

3

Describe the nation's financial cost on managing asthma

4

Discuss non-pharmacological and pharmacological treatment for asthma

5

Discuss therapeutic strategies for the treatment of difficult-to-treat and severe asthma



# Difficult-to-Treat and Severe Asthma

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Difficult-to-treat asthma is defined as asthma that is uncontrolled despite prescribing of medium or high dose ICS-LABA treatment to maintain good symptom control and reduce exacerbations

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Severe asthma is defined as asthma that is uncontrolled despite adherence with optimized high-dose ICS –LABA therapy and treatment of contributory factors or that worsens when high dose treatment is decreased



# Epidemiology

Asthma affects more than 22 million people

- 6 million children

Deaths due to asthma has declined, although the increasing prevalence of the disease

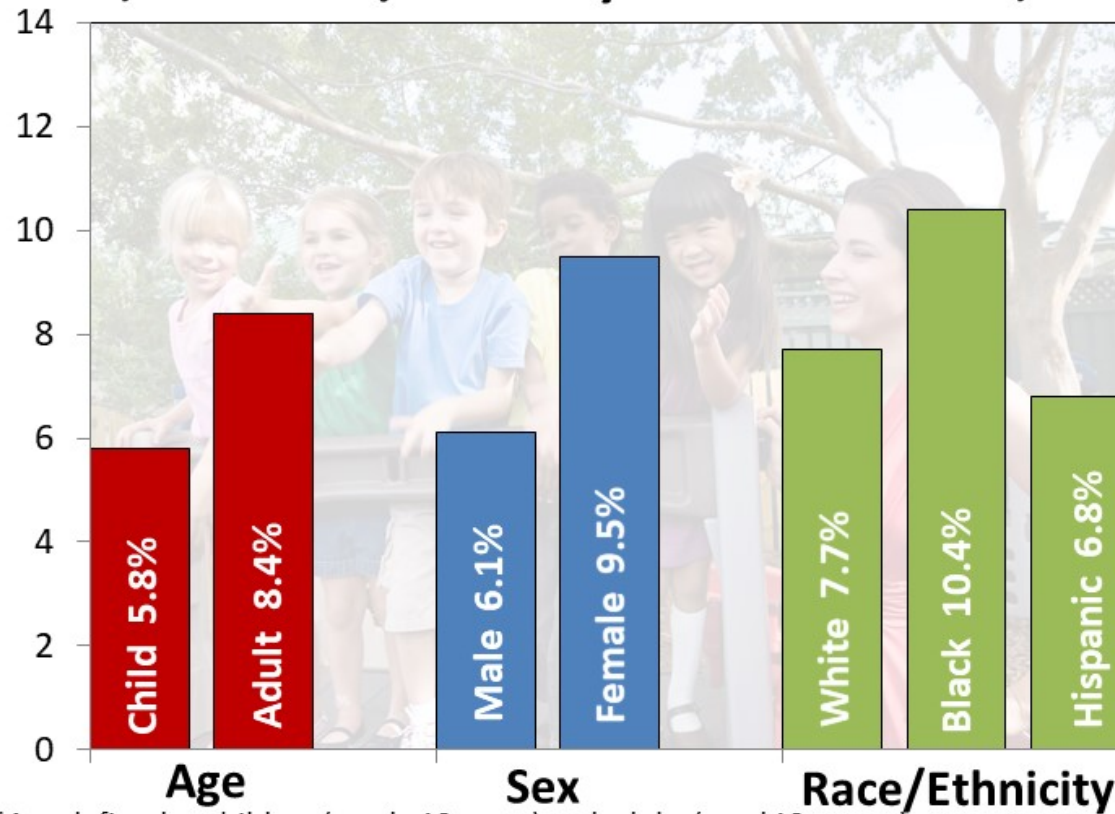
24% High intensity treatment

17% Difficult-to-Treat asthma

3.7% Severe asthma



## Percentage of People With Current Asthma by Age<sup>1</sup>, Sex<sup>2,3</sup>, and Race/Ethnicity<sup>3</sup>: United States, 2020



<sup>1</sup>Age defined as children (aged <18 years) and adults (aged 18+ years)

<sup>2</sup>Sex is defined as persons who answered “male” or “female” to the question “Are you male or female?”

<sup>3</sup>Sex and race/ethnicity include all ages

**Source: National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention**

Data, statistics, and surveillance. Centers for Disease Control and Prevention. <https://www.cdc.gov/asthma/asthmadata.htm>. Published May 25, 2022.



## Healthcare Utilization and Cost

Patients with severe asthma account for approximately 60% of costs

High costs due to:

- Medications
- Hospitalizations
- Physician visits
- Costs of oral steroid side effects

2022 Gina Main Report - Global Initiative for Asthma. GINA. <https://ginasthma.org/gina-reports/>. Published July 3, 2022.



# Pathophysiology

## Airflow limitation caused by changes in the airway

- Bronchoconstriction- bronchial smooth muscle contraction
- Airway Edema- inflammation, mucus hypersecretion and the formation of inspissated mucus plugs
- Airway hyper responsiveness- exaggerated bronchoconstrictor response to a wide variety of stimuli
- Airway remodeling- thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation



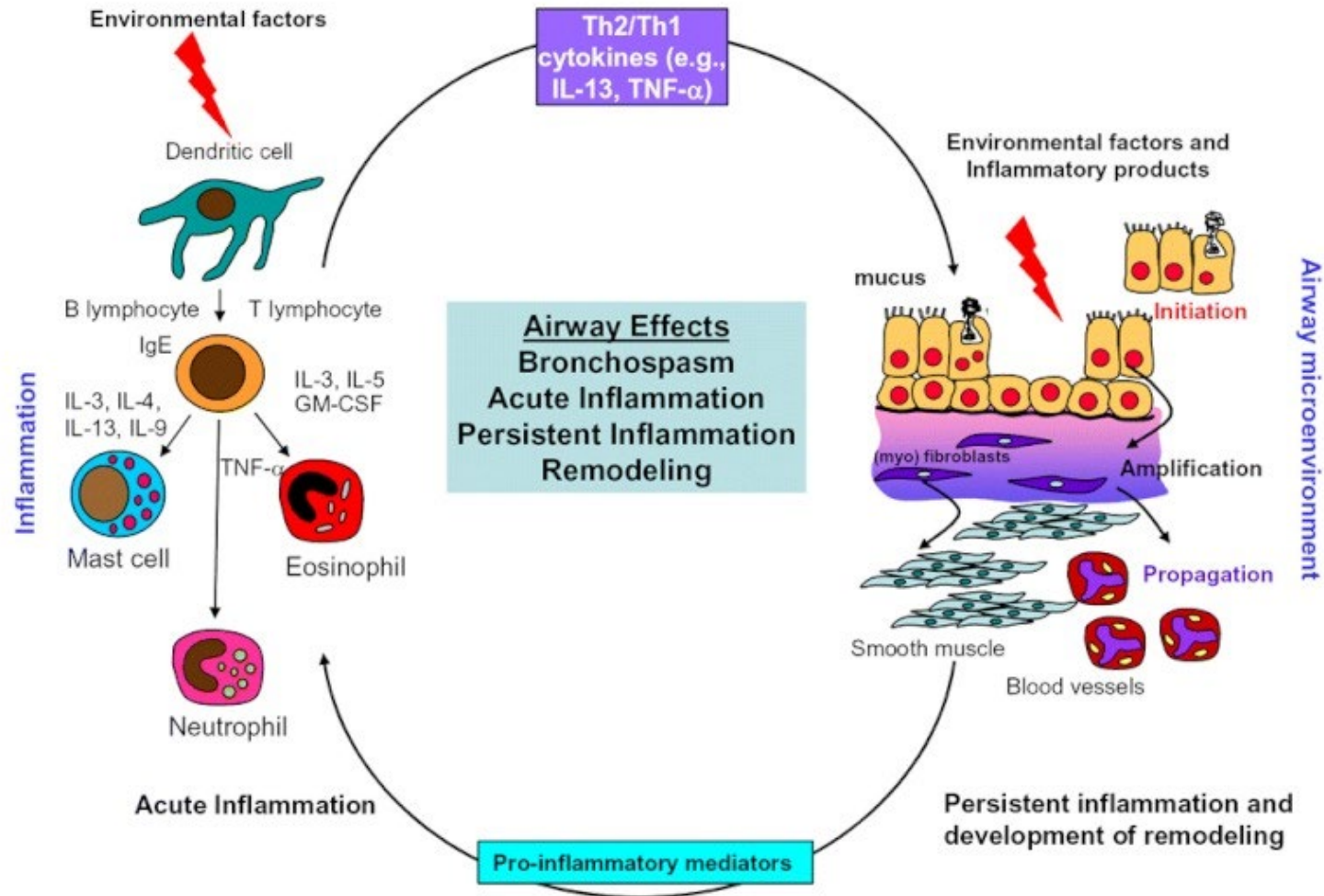
# Pathophysiology

## Immunohistopathologic features that causes inflammation:

- Neutrophils (especially in sudden-onset, fatal asthma exacerbations; occupational asthma, and patients who smoke)
- Eosinophils
- Lymphocytes
- Mast cell activation
- Epithelial cell injury







Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF- $\alpha$ , tumor necrosis factor-alpha

Section 2, definition, pathophysiology and pathogenesis of asthma, and ... <https://www.ncbi.nlm.nih.gov/books/NBK7223/>. Accessed July 13, 2022.



# Assessment and Management of Difficult-to-Treat and Severe Asthma

## Primary-Care and/or Specialist Care

- Confirm diagnosis
- Look for contributing factors
- Optimize management
- Review response after 3-6 months

## Specialist Care

- Investigate further and provide patient support
- Assess severe asthma phenotypes
- Consider other treatments
- Consider add-on biologic Type 2-targeted treatments



# Diagnosis

Perform	Perform spirometry before and after bronchodilator
Check	Check full flow-volume curve to assess for upper airway obstruction
Provide	If spirometry is normal, provide patient with peak flow meter and diary
Consider	Consider bronchial provocation testing if patient is able to withhold bronchodilators`



# Factors Contributing to Symptoms and Exacerbations

Incorrect  
inhaler  
technique

Suboptimal  
adherence

Comorbidities

Triggers

Over-use of  
SABAs

Medication  
Side Effects



## Goals of Therapy

To achieve good symptom control

To minimize future risk of

- Asthma-related mortality
- Exacerbations
- Persistent airflow limitation
- Side-effects of treatment



# Non-Pharmacological Management

Smoking  
cessation

Physical  
exercise

Healthy diet

Weight loss

Mucus  
Clearance  
Strategies

Influenza  
Vaccine

Breathing  
Exercises

Allergen  
Avoidance



# Pharmacological Treatment

## Controller Therapy

- Medium or High-dose ICS

## Reliever Therapy

- SABA
- ICS and LABA

## Add-On Therapy

- Non-biologics (LABA, LAMA, Leukotriene modifiers)
- Biologics (Anti-IgE, Anti-IL5/5R, Anti-IL4R, Anti-TSLP )



# Biologics

Anti-IgE (omalizumab)

Anti-IL5 (mepolizumab, reslizumab)

Anti-IL5R (benralizumab)

Anti-IL4R (dupilumab)

Anti-TSLP (tezepelumab)





## Xolair<sup>®</sup> (omalizumab)

Indication: patients 6 years old older with severe allergic asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen

Dosing: 75 to 375 mg subcutaneous injection every 2 or 4 weeks

Mechanism of Action: inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and dendritic cells, resulting in FcεRI down-regulation on these cells

Side Effects: arthralgia, general pain, fatigue, dizziness, fracture, pruritus, dermatitis, and earache



# Nucala<sup>®</sup> (mepolizumab)

Indication: patients 6 years and older with severe asthma and with an eosinophilic phenotype

## Dosing:

- adults and adolescents 12 years and older- 100 mg subcutaneous injection administered once every 4 weeks
- pediatric patients 6 to 11 years- 40 mg subcutaneous injection administered once every 4 weeks

Mechanism of Action: IL-5 antagonist (IgG1 kappa) inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface

Side Effects: headache, injection site reaction, back pain, and fatigue



## Cinqair<sup>®</sup> (reslizumab)

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Indication: patients 18 years and older with severe asthma and an eosinophilic phenotype

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Dosing: 3 mg/kg intravenous infusion once every 4 weeks

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Mechanism of Action: binds to IL-5, while inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil surface

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Side Effects: oropharyngeal pain and malignancy



# Fasenra<sup>®</sup> (benralizumab)

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Indication: patients 12 years and older with severe asthma and eosinophilic phenotype

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Dosing: 30mg subcutaneous injection administered once every 4 weeks for the first 3 doses, and then once every 8 weeks

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Mechanism of Action: monoclonal antibody (IgG1, kappa) that binds to the alpha subunit of the human interleukin-5 receptor (IL-5R $\alpha$ ) leading to apoptosis of eosinophils and basophils

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Side Effects: headache and pharyngitis



## Dupixent<sup>®</sup> (dupilumab)

Indication: patients 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma

### Dosing:

- adults and adolescents 12 years and older- initial dose of 400 mg then 200 mg given every other week or initial dose of 600 mg then 300 mg given every other week
- pediatric patients 6 to 11 years- 100 to 200mg every other week or 300 mg every four weeks

Mechanism of Action: monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by binding to the IL-4R $\alpha$  subunit

Side Effects: injection site reaction, oropharyngeal pain, and eosinophilia



# Tespire<sup>®</sup> (tezepelumab)

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Indication: adult and pediatric patients 12 years and older with severe asthma

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Dosing: 210 mg subcutaneous injection administered once every 4 weeks

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Mechanism of Action: thymic stromal lymphopoietin (TSLP) blocker monoclonal antibody IgG2 $\lambda$  that binds to human TSLP and blocks its interaction with the heterodimeric TSLP receptor

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Side Effects: pharyngitis, arthralgia, and back pain



# Comparison of Biologics

Agent	Route of Administration	Cost	Population	Phenotype
omalizumab	subcutaneous	1,295 per injection	Children (6) and adults	N/A
mepolizumab	subcutaneous	3,272 per injection	Children (6) and adults	eosinophilic phenotype
reslizumab	intravenous	1,071 per injection	Adults only	eosinophilic phenotype
benralizumab	subcutaneous	5.197 per injection	Children (12) and adults	eosinophilic phenotype
dupilumab	subcutaneous	3,573 per injection	Children (6) and adults	eosinophilic phenotype or OCS dependent
tezepelumab	subcutaneous	3,633 per injection	Children (12) and adults	N/A



# Monitoring



## Review response

Symptom control  
Type 2 comorbidities  
Treatment intensity



## Continue to optimize treatment

Review patient every 3-6 months  
Address patient concerns, assess risk factors,  
review response





## Conclusion

- Difficult-to-treat and severe asthma affects approximately 20% of patients with asthma.
- It is very important to properly assess the patients to provide adequate management.
- There are many add on therapy options that can be used to help aid the patient in asthma control.
- Patient's therapeutic regimen should always be assessed and monitored.



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Thank you

