

Rethinking Asthma

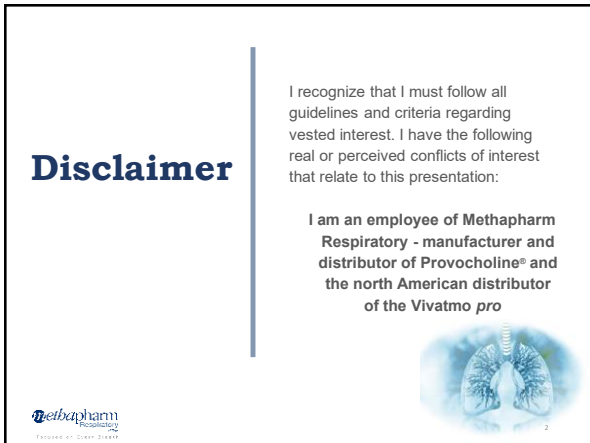
Endotypes
and
Phenotypes

Methapharm
Respiratory

Focused on Every Breath

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Disclaimer

I recognize that I must follow all guidelines and criteria regarding vested interest. I have the following real or perceived conflicts of interest that relate to this presentation:

I am an employee of Methapharm Respiratory - manufacturer and distributor of Provocholine® and the north American distributor of the Vivatmo pro

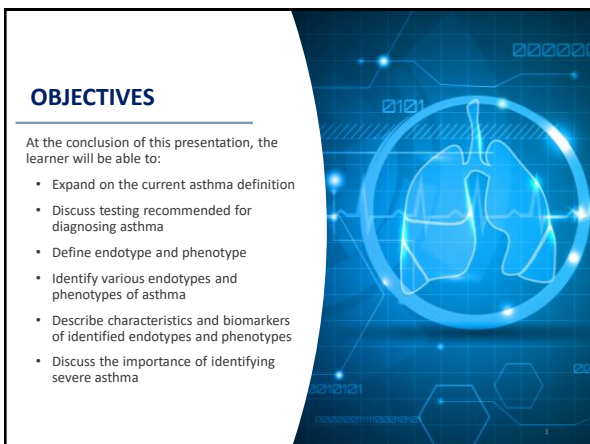


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OBJECTIVES

At the conclusion of this presentation, the learner will be able to:

- Expand on the current asthma definition
- Discuss testing recommended for diagnosing asthma
- Define endotype and phenotype
- Identify various endotypes and phenotypes of asthma
- Describe characteristics and biomarkers of identified endotypes and phenotypes
- Discuss the importance of identifying severe asthma




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Question 1

Asthma is a _____ disease.

- A. Heterogeneous
- B. Homogeneous



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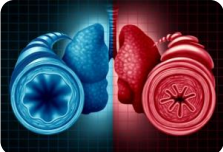
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Question 1

Asthma is a _____ disease.

- A. **Heterogeneous**
- B. Homogeneous




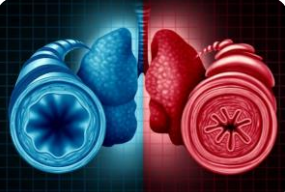
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Current Definition of Asthma

"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is 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 limitation."




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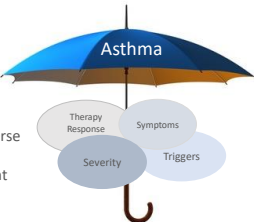
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Expanding the Definition of Asthma



Asthma is:

- an umbrella diagnosis
- no longer considered a single entity
- a heterogeneous disease – diverse in history, triggers, severity and responsiveness for every patient




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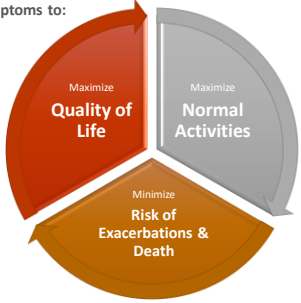
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Successful Asthma Management



Control symptoms to:



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Expanding the Definition of Asthma

What is changing?

- Different asthma phenotypes and differences in responsiveness to treatment
- Linking pathobiology to phenotype
- Precision/ targeted medical treatment



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Biology 101

GENOTYPE

PHENOTYPE

ENDOTYPE

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Psychology
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Biology 101

GENOTYPE

- Blueprint
- Instructions
- Genetic Makeup
- Variety

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Biology 101

PHENOTYPE

- Hair
- Eyes
- Height
- Complexion

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Psychology
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Biology 101

ENDOTYPE

The subtype of a condition, which is defined by a distinct functional or pathobiological mechanism.

With asthma there is no consensus on how to identify or treat a given endotype.



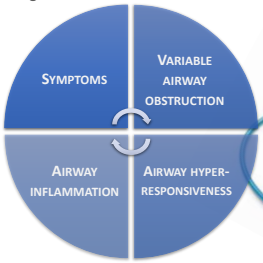
The iceberg illustration shows a small portion of the iceberg above the water line and a much larger, jagged portion submerged below the surface, symbolizing that the visible part of a condition is only a fraction of the total underlying pathology.

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ATS/ERS - Diagnosing Asthma

Diagnosing asthma includes four domains:



The diagram is a circle divided into four quadrants: SYMPTOMS (top-left), VARIABLE AIRWAY OBSTRUCTION (top-right), AIRWAY INFLAMMATION (bottom-left), and AIRWAY HYPER-RESPONSIVENESS (bottom-right). A central circular icon with arrows indicates a cyclical relationship between these domains.



A small illustration of human lungs is shown above a stethoscope.

No single domain is essential to the diagnosis and access to objective testing of all four domains is variable.


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Question 2

What is the first test to perform on a patient reporting asthma-type history & symptoms?

- A. CBC
- B. Spirometry pre and post bronchodilator
- C. Chest xray
- D. Bronchial challenge test



A small illustration of human lungs is shown in the top right corner.

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Question 2



What is the first test to perform on a patient reporting asthma-type history & symptoms?

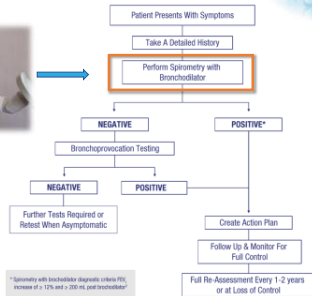
- A. CBC
- B. Spirometry pre and post bronchodilator
- C. Chest xray
- D. Bronchial challenge test

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Is It Asthma ?



Did you know....



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Diagnosing Asthma



What is the common practice?

Research finds that diagnosis is often based on symptoms alone:

- wheezing
- shortness of breath
- cough

The diagnosis is not being confirmed with objective testing!



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Is It Asthma ?

Did you know....

```

    graph TD
      A[Patient Presents With Symptoms] --> B[Take A Detailed History]
      B --> C[Perform Spirometry with Bronchodilator]
      C --> D[NEGATIVE]
      C --> E[POSITIVE*]
      D --> F[Branchprovocation Testing]
      F --> G[NEGATIVE]
      F --> H[POSITIVE]
      G --> I[Further Tests Required or Retest When Asymptomatic]
      H --> J[Create Action Plan]
      E --> J
      J --> K[Follow Up & Monitor For Full Control]
      K --> L[Full Re-Assessment Every 1-2 years or at Loss of Control]
  
```

*Spirometry with bronchodilator diagnostic criteria: FEV₁ increase of ≥ 12% and ≥ 200 mL post-bronchodilator

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Is It Asthma ?

Did you know....

```

    graph TD
      A[Patient Presents With Symptoms] --> B[Take A Detailed History]
      B --> C[Perform Spirometry with Bronchodilator]
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```

*Spirometry with bronchodilator diagnostic criteria: FEV₁ increase of ≥ 12% and ≥ 200 mL post-bronchodilator

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Is It Asthma ?

Bronchial Challenge Testing

```

    graph TD
      subgraph DirectTests [DIRECT TESTS]
        D1[METHACHOLINE]
        D2[HISTAMINE]
      end
      subgraph IndirectTests [INDIRECT TESTS]
        I1[EXERCISE TEST]
        I2[MANNITOL]
        I3[EUCAPNIC VOLUNTARY HYPERVENTILATION]
      end
      D1 --- L((Lungs))
      D2 --- L
      I1 --- L
      I2 --- L
      I3 --- L
  
```

*Spirometry with bronchodilator diagnostic criteria: FEV₁ increase of ≥ 12% and ≥ 200 mL post-bronchodilator

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Is It Asthma ?

Bronchial Challenge Testing

DIRECT TESTS

- METHACHOLINE
- HISTAMINE

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Is It Asthma ?

Bronchial Challenge Testing

INDIRECT TESTS

- EXERCISE TEST
- MANNITOL
- EUCAPNIC VOLUNTARY HYPERVENTILATION

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Is It Asthma ?

Did you know....

Indirect challenge test?

```

    graph TD
      A[Patient Presents With Symptoms] --> B[Take A Detailed History]
      B --> C[Perform Spirometry with Bronchodilator]
      C --> D{ }
      D --> E[NEGATIVE]
      D --> F[POSITIVE*]
      E --> G[Bronchoprovocation Testing]
      G --> H{ }
      H --> I[NEGATIVE]
      H --> J[POSITIVE]
      I --> K[Further Tests Required or Retest When Asymptomatic]
      J --> L[Create Action Plan]
      L --> M[Follow Up & Monitor For Full Control]
      M --> N[Full Re-Assessment Every 1-2 years or at Loss of Control]
      F --> L
  
```

*Symmetry with bronchodilator diagnostic criteria (FEV1 increase of ≥ 12% and ≥ 200 mL, and/or bronchodilator)

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Global Initiative for Asthma



Asthma Severity

Mild

- Symptoms twice a month or more
- Symptoms not daily

Moderate

- Symptoms most days OR
- Waking with asthma once a week or more






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Question 3

It is necessary to distinguish between severe asthma and uncontrolled asthma

A. True
B. False






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Question 3

It is necessary to distinguish between severe asthma and uncontrolled asthma

A. **True**
B. False

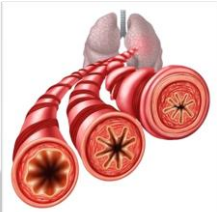



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Severe Asthma

ATS/ERS Joint Definition



Severe Asthma is "asthma which requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy."¹

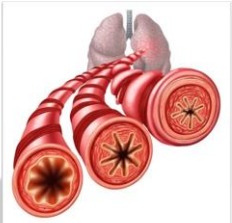

Of note – it is **necessary** to distinguish between severe asthma and uncontrolled asthma²




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Why Severe Asthma?




- Focus of research
- Smallest group of patients
- Highest healthcare utilization
- Most expensive group
- Long-term damage such as lung remodeling



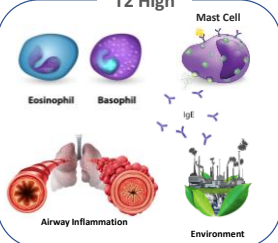
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Asthma Endotypes

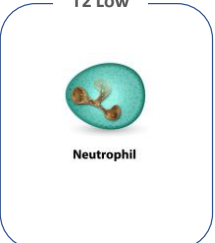


T2 High




Eosinophil, Basophil, Mast Cell, IgE, Airway Inflammation, Environment

T2 Low



Neutrophil



30

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Endotype Mechanistic Characteristics

T2 High

The diagram illustrates the T2 High endotype mechanism. It features a central Eosinophil cell. Surrounding it are Basophil and Mast Cell cells. Below the cells are two circular diagrams: 'Airway Inflammation' showing inflamed airways and 'Environment' showing a green landscape with trees and a sun. The entire diagram is enclosed in a rounded rectangle. In the top right corner of the slide, there is a small image of human lungs. The slide includes the AstraZeneca logo and the text 'AstraZeneca Respiratory' and 'FOCUS ON COPD 2025' in the bottom left corner, and the number '31' in the bottom right corner.

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T2-High Endotype

Eosinophils

- Affect various inflammatory cells
- Release inflammatory mediators including cytokines, chemokines, granule mediators and cysteinyl leukotrienes
- Associated with remodeling in the airways
- Support smooth muscle contraction and inhibit relaxation

Eosinophil

The slide features a list of four bullet points describing the role of eosinophils. To the right of the text is a detailed illustration of an eosinophil cell. In the top right corner, there is a small image of human lungs. The slide includes the AstraZeneca logo and the text 'AstraZeneca Respiratory' and 'FOCUS ON COPD 2025' in the bottom left corner, and the number '32' in the bottom right corner.

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Endotype Mechanistic Characteristics

T2 High

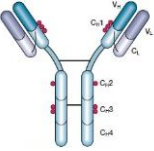

The diagram illustrates the T2 High endotype mechanism, similar to slide 31 but with a focus on IgE. It features a central Eosinophil cell. Surrounding it are Basophil and Mast Cell cells. In the center, several Y-shaped IgE antibodies are shown. Below the cells are two circular diagrams: 'Airway Inflammation' showing inflamed airways and 'Environment' showing a green landscape with trees and a sun. The entire diagram is enclosed in a rounded rectangle. In the top right corner of the slide, there is a small image of human lungs. The slide includes the AstraZeneca logo and the text 'AstraZeneca Respiratory' and 'FOCUS ON COPD 2025' in the bottom left corner, and the number '33' in the bottom right corner.

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T2-High Endotype

Immunoglobulin E (IgE)

- Marker for atopy
- May have role in airway remodeling
- Activates mast cells

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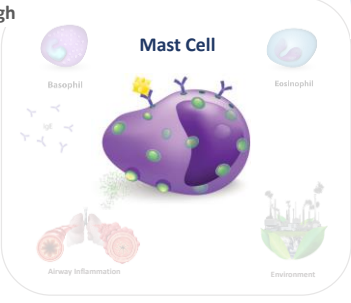

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Endotype Mechanistic Characteristics

T2 High

Mast Cell

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T2-High Endotype

Mast Cells

- Pathogenic role in asthma
- Tissue-based
- Secrete mediators: histamine, prostaglandin D2, cytokines, leukotrienes, and proteases
- Secreted mediators correlate with severity of disease

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Endotype Mechanistic Characteristics

T2 High

Eosinophil Mast Cell

Basophil

Airway Inflammation Environment

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T2-High Endotype

Basophils

- Pathogenic role in asthma
- Secrete mediators: histamine, prostaglandin D₂, cytokines, leukotrienes and interleukin 4
- Secreted mediators associated with disease severity
- Blood-borne but activated in the tissues
- See an increase of basophils in bronchial walls and tissue-based basophils are associated with allergic disease

Basophil

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Question 4

Eosinophils, Basophils, Mast Cells, IgE are _____ of Th2 High Asthma

A. Endotypes
B. Phenotypes
C. Characteristics


Eosinophil Basophil
Mast Cell

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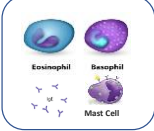
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Question 4



Eosinophils, Basophils, Mast Cells, IgE are _____ of Th2 High Asthma

- A. Endotypes
- B. Phenotypes
- C. **Characteristics**




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T2-High Phenotypes



- Early-Onset Allergic Asthma
- Late-Onset Eosinophilic Asthma
- Aspirin-Exacerbated Respiratory Disease (AERD)






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T2-High Phenotypes



- Early-Onset Allergic Asthma**
 - Classic phenotype
 - Extrinsic
- Late-Onset Eosinophilic Asthma
 - Adult onset, older with more severe
 - Often have high blood and sputum e
 - Airway inflammation not responsive
- Aspirin-Exacerbated Respiratory Disease (AERD)



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T2-High Phenotypes




Early-Onset Allergic Asthma

- Classic phenotype
- Extrinsic

Late-Onset Eosinophilic Asthma

- Adult onset, older with more severe disease
- Often have high blood and sputum eosinophilia
- Airway inflammation not responsive to ICS

Aspirin-Exacerbated Respiratory Disease (AERD)

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T2-High Phenotypes




Early-Onset Allergic Asthma

- Classic phenotype
- Extrinsic

Late-Onset Eosinophilic Asthma

- Adult onset, older with more severe disease
- Often have high blood and sputum eosinophilia
- Airway inflammation not responsive to ICS

Aspirin-Exacerbated Respiratory Disease (AERD)






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T2-High Phenotypes

Additional factors for Refractory T2-High

- Air pollution
- Cigarette Smoking
- Neurogenic Inflammation
- Viral infection

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Endotype Mechanistic Characteristics

T2 High

Eosinophil, Basophil, Mast Cell, IgE, Airway Inflammation, Environment

T2 Low

Neutrophil

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T2-Low Endotype

- Much less is known about T2-low.
- Most significantly, it is identified by the **absence** of the markers of T2-high.
- Does not respond to ICS therapy
- Severe neutrophilic asthma is associated with obesity, smoking, smooth muscle abnormalities.

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Pharmaceuticals
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Endotype Mechanistic Characteristics

T2 High

Eosinophil, Basophil, Mast Cell, IgE, Airway Inflammation, Environment

T2 Low

Neutrophil

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T2-Low Endotype

Neutrophils

- First line of defense
- Ingest and destroy invading microorganisms
- Increased airway neutrophilia correlates with lung decline
- Prominent in COPD



Neutrophil







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T2-Low Phenotypes

- Obesity
- Smoking-Associated
- Very Late Onset

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T2-Low Phenotypes

Obesity




- important risk factor for morbidity
- severe symptoms with moderate lung function

Smoking-Associated

- Considered T2-low neutrophilic
- Increases sensitization to allergens
- Increases total IgE

Very Late Onset

- >50 and >65: depends on the study

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T2-Low Phenotypes

Obesity


- important risk factor for morbidity
- severe symptoms with moderate lung function

Smoking-Associated

- Considered T2-low neutrophilic steroid-resistant
- Increases sensitization to allergens
- Increases total IgE

Very Late Onset

- >50 and >65: depends on the study



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T2-Low Phenotypes

Obesity


- important risk factor for morbidity
- severe symptoms with moderate lung function

Smoking-Associated

- Considered T2-low neutrophilic steroid-resistant
- Increases sensitization to allergens
- Increases total IgE

Very Late Onset

- >50 and >65: depends on the study




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Biomarkers



- NEUTROPHILS
- BASOPHILS
- EOSINOPHILS
- IGE (IMMUNOGLOBULIN E)
- PERIOSTIN
- FeNO (FRACTIONAL EXHALED NITRIC OXIDE)


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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin
- Exhaled nitric oxide (FeNO)




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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin
- Exhaled nitric oxide (FeNO)




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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin
- Exhaled nitric oxide (FeNO)





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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE**
- Serum / Blood Periostin
- Exhaled nitric oxide (FeNO)


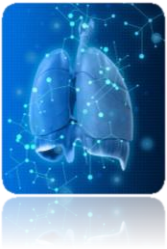
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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin**
- Exhaled nitric oxide (FeNO)


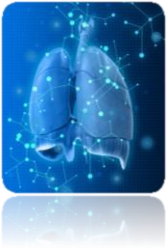
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Biomarkers

T2 High – Inflammation Endotype



- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin
- Exhaled Nitric Oxide (FeNO)**


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Measuring Biomarkers

T2 High – Inflammation



- Blood
- Sputum Cytometry
- Fractional exhaled nitric oxide (FeNO)




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Biomarkers



T2 Low



Have not been researched as much as T2-high.

Proposed biomarkers include:



- Blood or sputum neutrophils
- Metalloproteinase 9
- Cytokine IL-6



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Treatment of Endotypes





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Question 5

Biologic medications are currently indicated for _____, _____ patients.

- A. Moderate, Th2 high
- B. Moderate, Th2 low
- C. Severe, Th2 high
- D. Severe, Th2 low



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Question 5

Biologic medications are currently indicated for _____, _____ patients.

- A. Moderate, Th2 high
- B. Moderate, Th2 low
- C. **Severe, Th2 high**
- D. Severe, Th2 low



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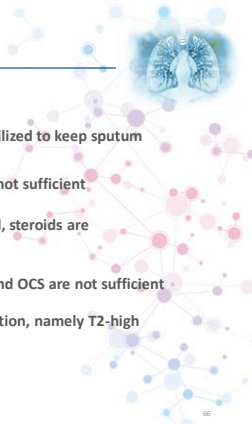

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Treatment of Endotypes

T2-High

- Inhaled corticosteroids should be utilized to keep sputum eosinophil counts below 3%
 - oral steroids are required if ICS is not sufficient.
- If eosinophil counts are not elevated, steroids are unwarranted
- Biologics are considered when ICS and OCS are not sufficient
- Several biologics target T2 inflammation, namely T2-high



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Treatment of Endotypes

6 Biologics

Adult (6)

IgE, IL4, IL5, IL13

Infusion

Injection

Pediatric (4)

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Treatment of Endotypes

Biologics

Endotype	Medication	Targets
T2 – High	Omalizumab	Anti – IgE
	Mepolizumab	Anti-IL5
	Reslizumab	Anti-IL5
	Dupilumab	Anti-IL4 and IL 13
	Benralizumab	Anti-IL5
	Tezepelumab	Not specified

T2 – High

Omalizumab

Anti – IgE

Mepolizumab

Anti-IL5

Reslizumab

Anti-IL5

Dupilumab

Anti-IL4 and IL 13

Benralizumab

Anti-IL5

Tezepelumab

Not specified

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Treatment of Endotypes

T2-low

- No biologics for T2-low asthma
- Macrolides have shown to be effective treatment

Endotype	Treatment	Targets
T2 – Low	Clarithromycin	Bacterial infections
	Azithromycin	Bacterial infections

T2 – low

No biologics for T2-low asthma

Macrolides have shown to be effective treatment

T2 – Low

Clarithromycin

Bacterial infections

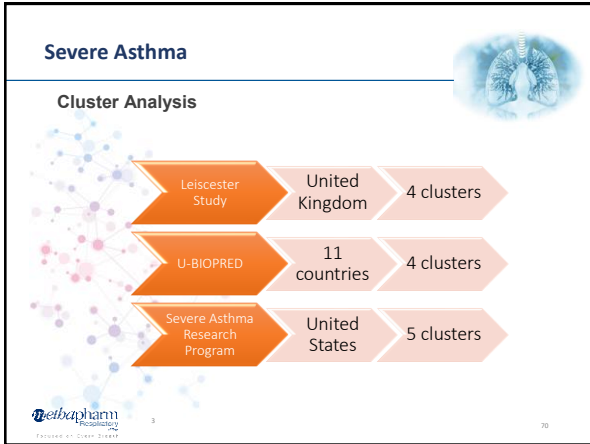
Azithromycin

Bacterial infections

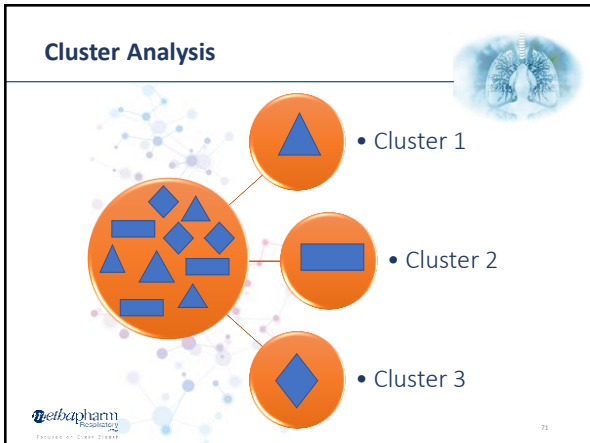
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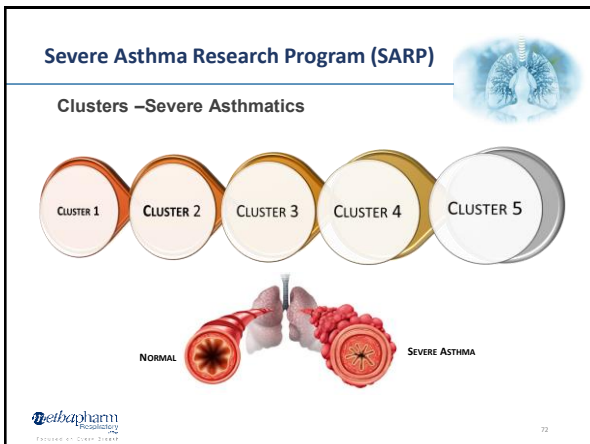
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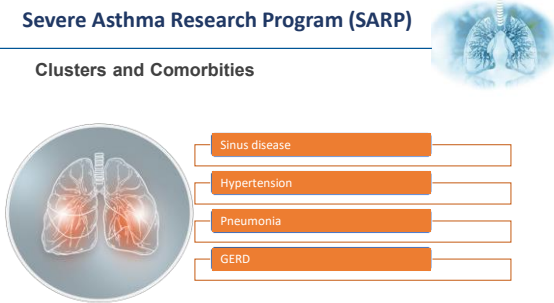
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Severe Asthma Research Program (SARP)

Clusters and Comorbidities



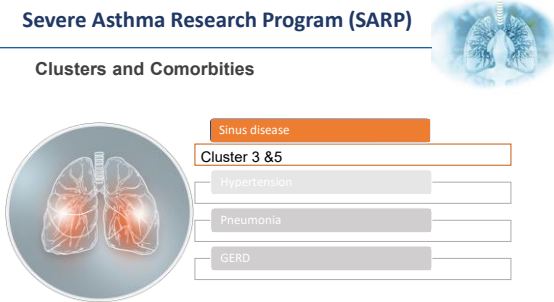
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- Hypertension
- Pneumonia
- GERD

GlaxoSmithKline
Respiratory
FOCUS ON CLEAR CARE

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Severe Asthma Research Program (SARP)

Clusters and Comorbidities



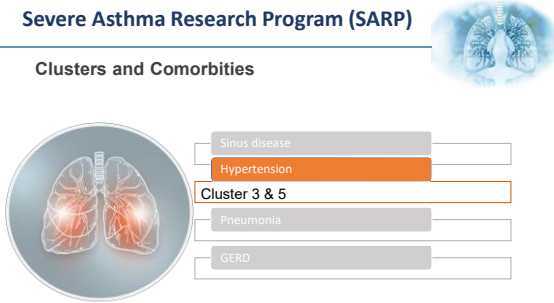
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- Cluster 3 & 5
- Hypertension
- Pneumonia
- GERD

GlaxoSmithKline
Respiratory
FOCUS ON CLEAR CARE

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Severe Asthma Research Program (SARP)

Clusters and Comorbidities



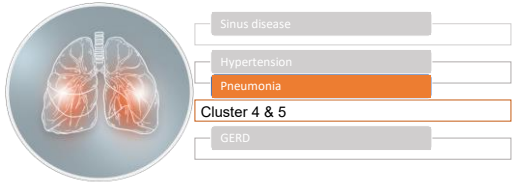
- Sinus disease
- Hypertension
- Cluster 3 & 5
- Pneumonia
- GERD

GlaxoSmithKline
Respiratory
FOCUS ON CLEAR CARE


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Severe Asthma Research Program (SARP)

Clusters and Comorbidities



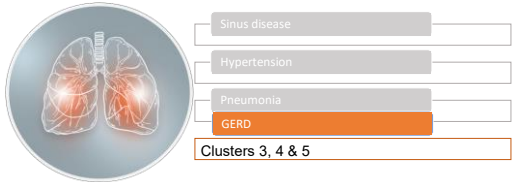
Sinus disease
 Hypertension
 Pneumonia
 Cluster 4 & 5
 GERD




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Severe Asthma Research Program (SARP)

Clusters and Comorbidities



Sinus disease
 Hypertension
 Pneumonia
 GERD
 Clusters 3, 4 & 5




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Severe Asthma Research Program (SARP)

Clusters and Characteristics

CLUSTER	Blood Eosinophils	FeNO	Serum IgE HIGH	Serum IgE LOW	Hyper-responsive to MCT HIGH	Hyper-responsive to MCT LOW	Sputum Inflammatory Cells HIGHEST	Eosinophil Elevated	Neutrophil HIGHEST
Cluster 1	X	X	X						
Cluster 2	X	X	X						
Cluster 3	X	X		X		X	X	X	
Cluster 4	X	X	X		X		X	X	
Cluster 5	X	X		X	X		X	X	X



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How Cluster Analysis May Help



Clusters –Severe Asthmatics



- The clusters highlight the disease heterogeneity of asthma
- The different phenotypes suggest different pathophysiologic processes and may assist in prescribing therapy and enhance asthma control
- The algorithm applied to the study subjects was successful in assigning 80% of the subjects to the appropriate cluster

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Diagnostic Journey



- Asthma is heterogenous and may change.
- What works for one does not work for all.
- Diagnosis may be a maze
- Accurate diagnosis = correct treatment

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SUMMARY

- Asthma is not simply asthma
- Research is providing increasingly specific targets for asthma therapies
- Through identification of asthma endotypes and phenotypes we can offer precise therapies which decrease medication side-effects, exacerbations, emergency visits, hospitalizations, lung function decline, and increase lung function and quality of life



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We welcome your questions!



thank you!

@ hmurgatroyd@methapharm.com

1-833-887-7686

www.methapharmrespiratory.com



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