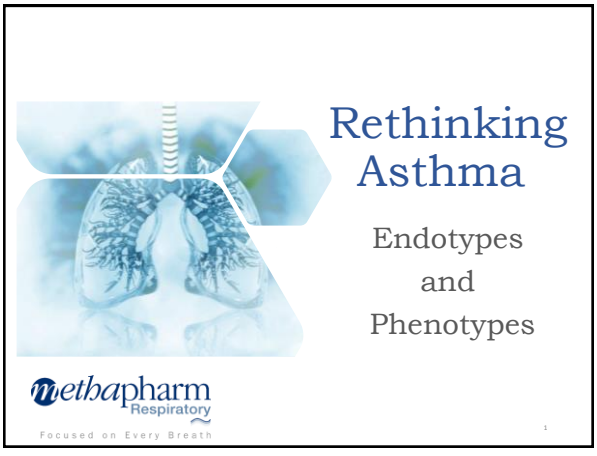
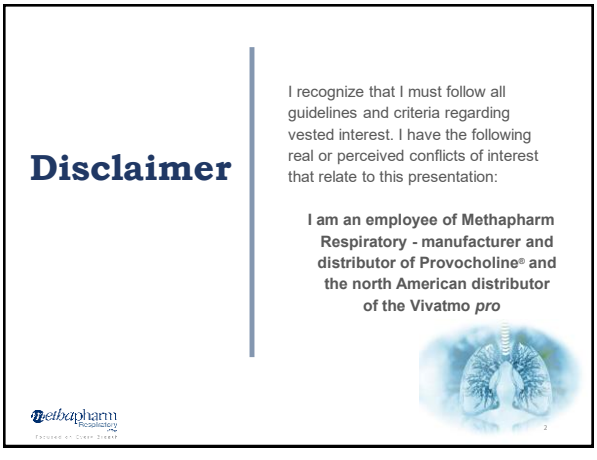
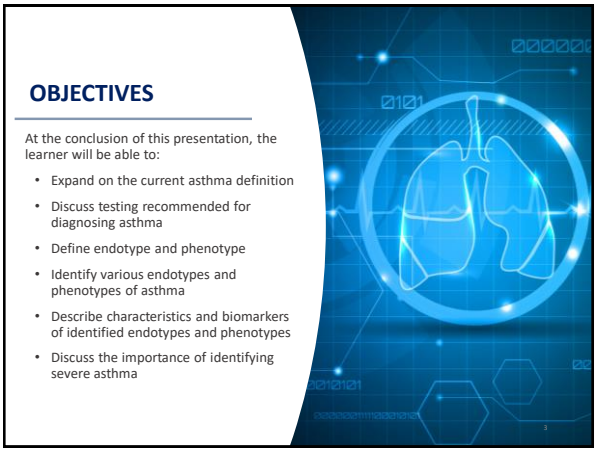

Rethinking Asthma
Endotypes and Phenotypes
methapharm Respiratory
Focused on Every Breath
1

1


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
methapharm Respiratory
2

2


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
3

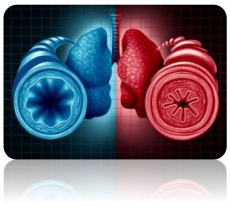
3

Question 1

Asthma is a _____ disease.

A. Heterogeneous

B. Homogeneous



4

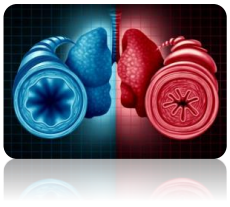
4

Question 1

Asthma is a _____ disease.

A. Heterogeneous

B. Homogeneous

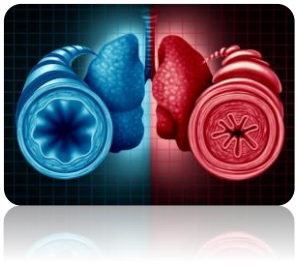


5

5

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."



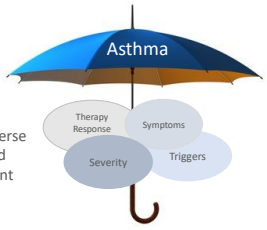
6

6

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

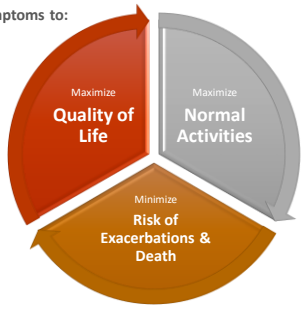


7

7

Successful Asthma Management

Control symptoms to:



8

8

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

9

9

Biology 101

GENOTYPE

PHENOTYPE

ENDOTYPE

10

Biology 101

GENOTYPE

- Blueprint
- Instructions
- Genetic Makeup
- Variety

11

Biology 101

PHENOTYPE

- Hair
- Eyes
- Height
- Complexion

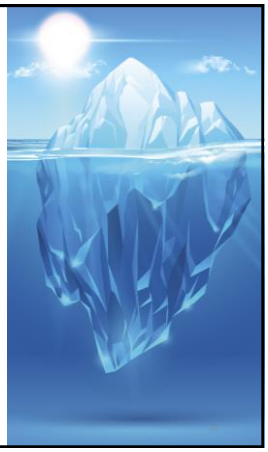
12

Biology 101

ENDOTYPE

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

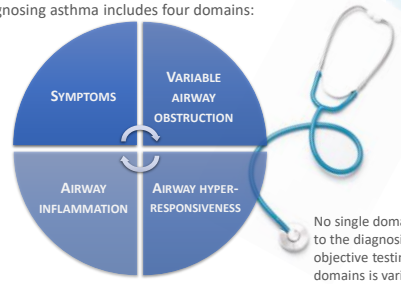
With asthma there is no consensus on how to identify or treat a given endotype.



13

ATS/ERS - Diagnosing Asthma

Diagnosing asthma includes four domains:



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

14

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

15

Question 2

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

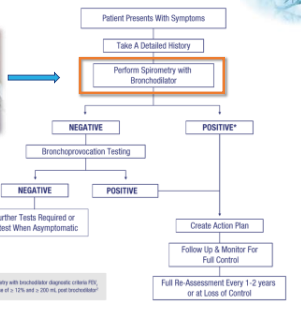
A. CBC
B. Spirometry pre and post bronchodilator
C. Chest xray
D. Bronchial challenge test

16

16

Is It Asthma ?

Did you know....



17

17

Diagnosing Asthma

What is the common practice?

Research finds that diagnosis is often based on **symptoms alone**:

- wheezing
- shortness of breath
- cough

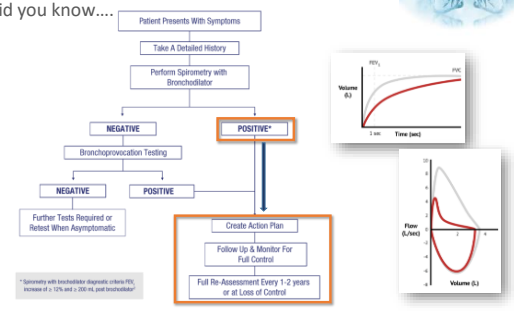
The diagnosis is not being confirmed with objective testing!

18

18

Is It Asthma ?

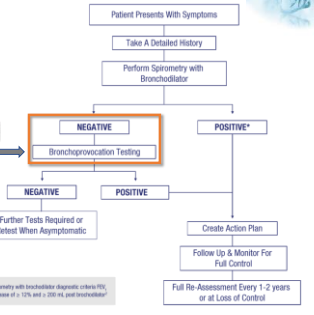
Did you know....



19

Is It Asthma ?

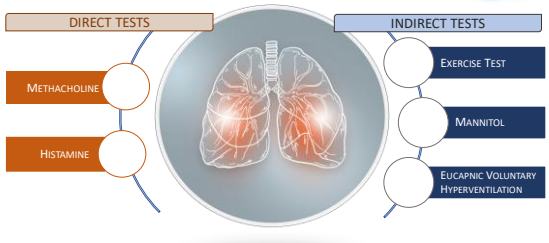
Did you know....



20

Is It Asthma ?

Bronchial Challenge Testing



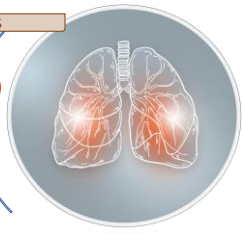
21

Is It Asthma ?

Bronchial Challenge Testing

DIRECT TESTS

- METHACHOLINE
- HISTAMINE



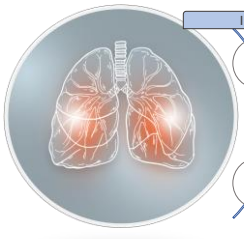
22

Is It Asthma ?

Bronchial Challenge Testing

INDIRECT TESTS

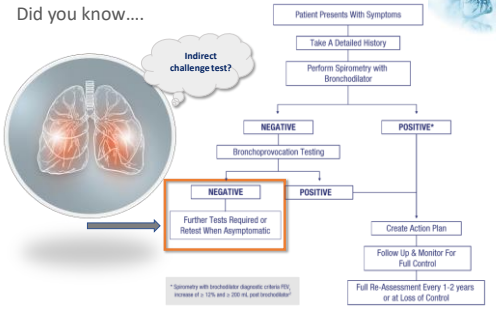
- EXERCISE TEST
- MANNITOL
- EUCAPNIC VOLUNTARY HYPERVENTILATION



23

Is It Asthma ?

Did you know....



24

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

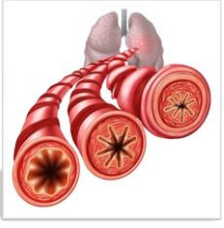
25

25

Question 3

It is necessary to distinguish between severe asthma and uncontrolled asthma

A. True
B. False



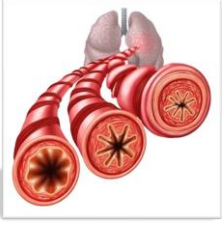
26

26

Question 3

It is necessary to distinguish between severe asthma and uncontrolled asthma

A. True
B. False

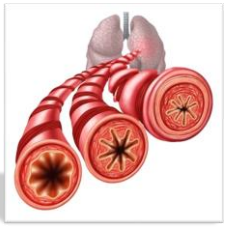


27

27

Severe Asthma

ATS/ERS Joint Definition



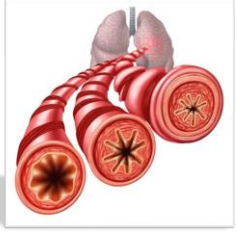
Severe Asthma is "asthma which requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy."[1]

Of note – it is ***necessary*** to distinguish between severe asthma and uncontrolled asthma[2]

28

28

Why Severe Asthma?

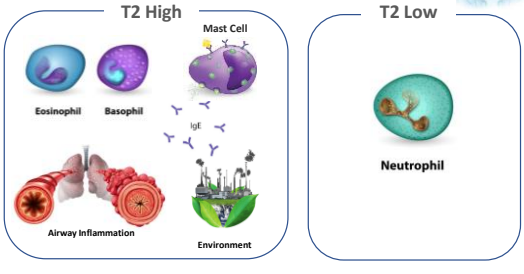


- Focus of research
- Smallest group of patients
- Highest healthcare utilization
- Most expensive group
- Long-term damage such as lung remodeling

29

29

Asthma Endotypes

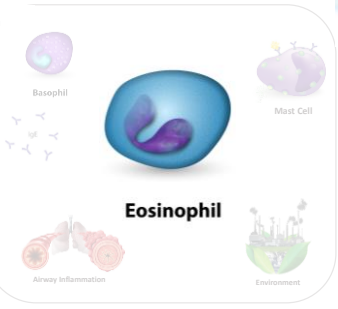


30

30

Endotype Mechanistic Characteristics

T2 High

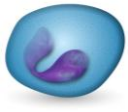


31

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

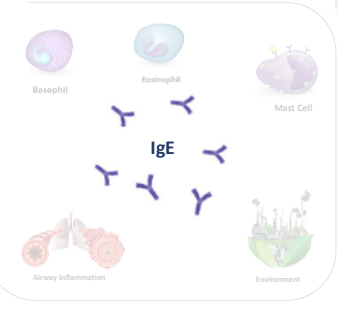


Eosinophil

32

Endotype Mechanistic Characteristics

T2 High

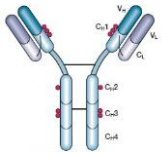


33

T2-High Endotype

Immunoglobulin E (IgE)

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

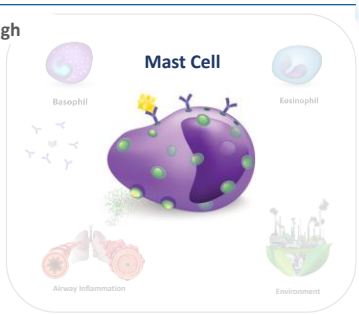


34

34

Endotype Mechanistic Characteristics

T2 High



35

35

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

Mast Cell

36

36

Endotype Mechanistic Characteristics

T2 High

37

37

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

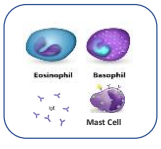
38

38

Question 4

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

A. Endotypes
B. Phenotypes
C. Characteristics



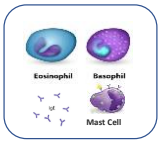
39

39

Question 4

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

A. Endotypes
B. Phenotypes
C. Characteristics



40

40

T2-High Phenotypes

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

41

41

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)

42

42

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)

43

43

T2-High Phenotypes

Early-Onset Allergic Asthma
- Classic phenotype
- Extrinsic

Late-Onset Eosinophilic Asthma
- Adult onset, older with more severe dise
- Often have high blood and sputum eosin
- Airway inflammation not responsive to ICS

Aspirin-Exacerbated Respiratory Disease (AERD)

44

44

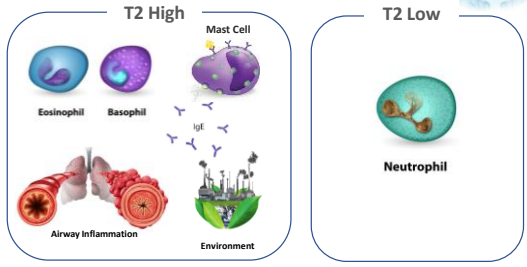
T2-High Phenotypes

Additional factors for Refractory T2-High
- Air pollution
- Cigarette Smoking
- Neurogenic Inflammation
- Viral infection

45

45

Endotype Mechanistic Characteristics



46

46

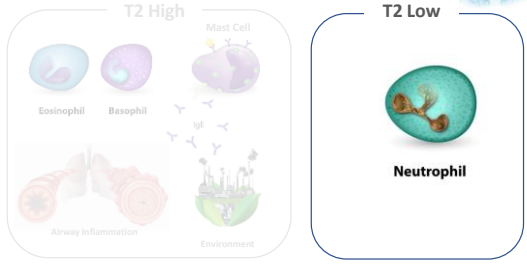
T2-Low Endotype

- 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.

47

47

Endotype Mechanistic Characteristics



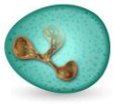
48

48

T2-Low Endotype

Neutrophils

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



Neutrophil

49

49

T2-Low Phenotypes

- **Obesity**
- **Smoking-Associated**
- **Very Late Onset**

50

50

T2-Low Phenotypes

Obesity

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

Smoking-Associated

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

Very Late Onset

- >50 and >65: depends on the study

51

51

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

52

52

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

53

53

Biomarkers

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

54

54

Biomarkers

T2 High – Inflammation Endotype

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

55

55

Biomarkers

T2 High – Inflammation Endotype

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

56

56

Biomarkers

T2 High – Inflammation Endotype

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

57

57

Biomarkers

T2 High – Inflammation Endotype

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

58

58

Biomarkers

T2 High – Inflammation Endotype

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

59

59

Biomarkers

T2 High – Inflammation Endotype

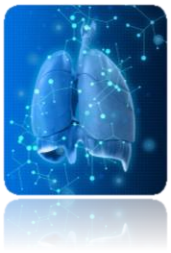
- Blood Eosinophils
- Airway or Peripheral Eosinophils
- Serum IgE / Allergy-Specific IgE
- Serum / Blood Periostin
- **Exhaled Nitric Oxide (FeNO)**

60

60

Measuring Biomarkers

T2 High – Inflammation



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

61

Biomarkers

T2 Low

Have not been researched as much as T2-high.

Proposed biomarkers include:

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

62

Treatment of Endotypes

63

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

64

64

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

65

65

Treatment of Endotypes

T2-High

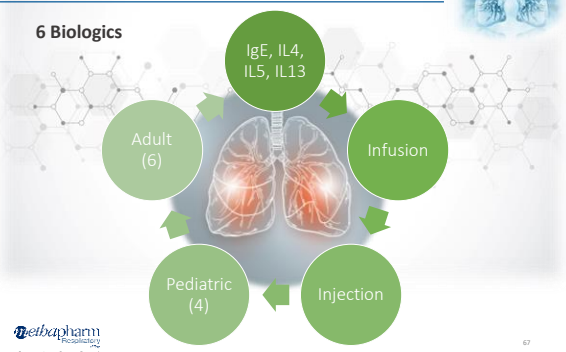
- **Inhaled corticosteroids should be utilized to keep sputum eosinophil counts below 3%**
  - **oral steroids are required if ICS is not sufficient**
- **If eosinophil counts are not elevated, steroids are unwarranted**
- **Biologics are considered when ICS and OCS are not sufficient**
- **Several biologics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

66

66

Treatment of Endotypes

6 Biologics



67

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

68

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

69

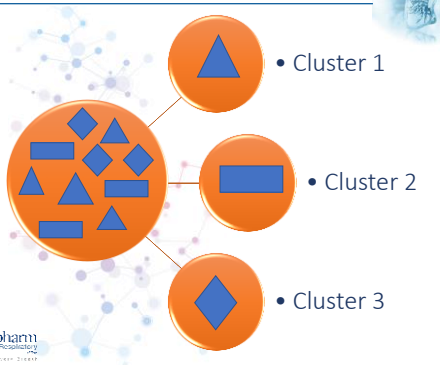
Severe Asthma

Cluster Analysis

Leiscester Study	United Kingdom	4 clusters
U-BIOPRED	11 countries	4 clusters
Severe Asthma Research Program	United States	5 clusters

70

Cluster Analysis

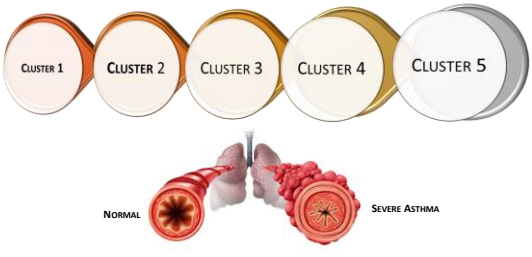


- Cluster 1
- Cluster 2
- Cluster 3

71

Severe Asthma Research Program (SARP)

Clusters –Severe Asthmatics



72

Severe Asthma Research Program (SARP)

Clusters and Comorbities

- Sinus disease
- Hypertension
- Pneumonia
- GERD

73

Severe Asthma Research Program (SARP)

Clusters and Comorbities

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

74

Severe Asthma Research Program (SARP)

Clusters and Comorbities

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

75

Severe Asthma Research Program (SARP)

Clusters and Comorbities

- Sinus disease
- Hypertension
- Pneumonia
- Cluster 4 & 5
- GERD

76

Severe Asthma Research Program (SARP)

Clusters and Comorbidities

- Sinus disease
- Hypertension
- Pneumonia
- GERD
- Clusters 3, 4 & 5

77

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

78

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

79

79

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

80

80

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

81

81

We welcome your questions!

thank you!

hmurgatroyd@methapharm.com

1-833-887-7686

www.methapharmrespiratory.com

82

82

REFERENCES

An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Helen K. Reddel, D. Robin Taylor, Eric D. Bateman, et. Al. Am J Respir Crit Care Med Vol 180. pp 59–99, 2009 DOI: 10.1164/rccm.200801-060ST

Bostantzoglou C, Delimpoura V, Samitas K, et al. Clinical asthma phenotypes in the real world: opportunities and challenges. Breathe 2015; 11: 186–193

Chung KF, Wenzel SE, Brozek JL; ERS/ATS Task Force on Definition, Evaluation and Treatment of Severe Asthma. Eur Respir J. 2014 Jul;44(1):267-8. doi: 10.1183/09031936.00064614

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

Fajt, M.L, and Wenzel, S.E. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. J Allergy Clin Immunol. February 2015.

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginasthma.org

Kuruvilla, M.E., Eun-Hyung Lee, F., Lee, G.B.. Understanding Asthma Phenotypes, Endotypes and Mechanisms of Disease. Clin Rev Allergy Immunol. April 2019; 56(2): 219-233. doi:10.1007/s12-16-018-8712-1.

Moore, W.C., et al. Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med Vol 181. pp 315-323, 2010

Svenningsen S and Nair P (2017) Asthma Endotypes and an Overview of Targeted Therapy for Asthma. Front. Med. 4:158. doi: 10.3389/fmed.2017.0015

To et al. BMC family Practice (2015) 16:19 DOI 10.1186/s12875-015-0232-y

83

83