Evoluzione dell'asma

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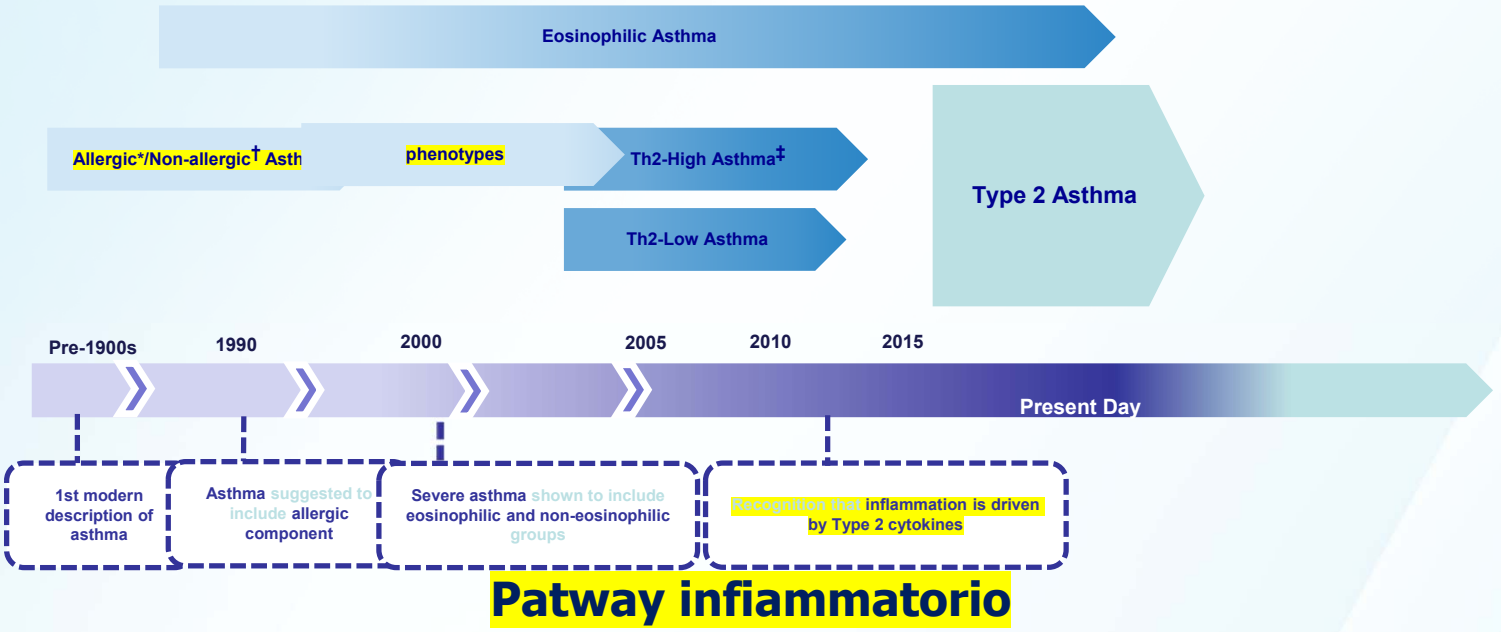
The Understanding of Asthma and Phenotyping Has Evolved Over the Years[1,2]



IgE=immunoglobulin E; Th2=T helper type 2 cell.
*Due to allergens from outside the body and associated with environmental exposures, atopy, and other allergic diseases. †Due to factors intrinsic to the body, present regardless of season/environment, and lacking atopy. ‡Associated with consistent clinical and inflammatory characteristics (increased blood and airway eosinophilia, airway hyperresponsiveness, thickened subepithelial basement membrane, higher IgE levels, and higher tissue expression of IL-5 and IL-13).
1. Gauthier M, et al. *Am J Respir Crit Care Med*. 2015;192(6):660-668. 2. Fahy JV. *Nat Rev Immunol*. 2015;15(1):57-65.

Personalized Medicine in Allergy

Matteo Ferrando,[1] Diego Bagnasco,[1] Gilda Varricchi,[2] Stefano Bernardi,[1] Alice Bragantini,[1] Giovanni Passalacqua,[1] Giorgio Walter Canonica[1]*

[1]*Allergy & Respiratory Diseases, DIMI Department of Internal Medicine, IRCCS AOU San Martino-IST, University of Genoa, Genoa, Italy*
[2]*Division of Clinical Immunology and Allergy, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy*

Review
Allergy Asthma Immunol Res. 2016

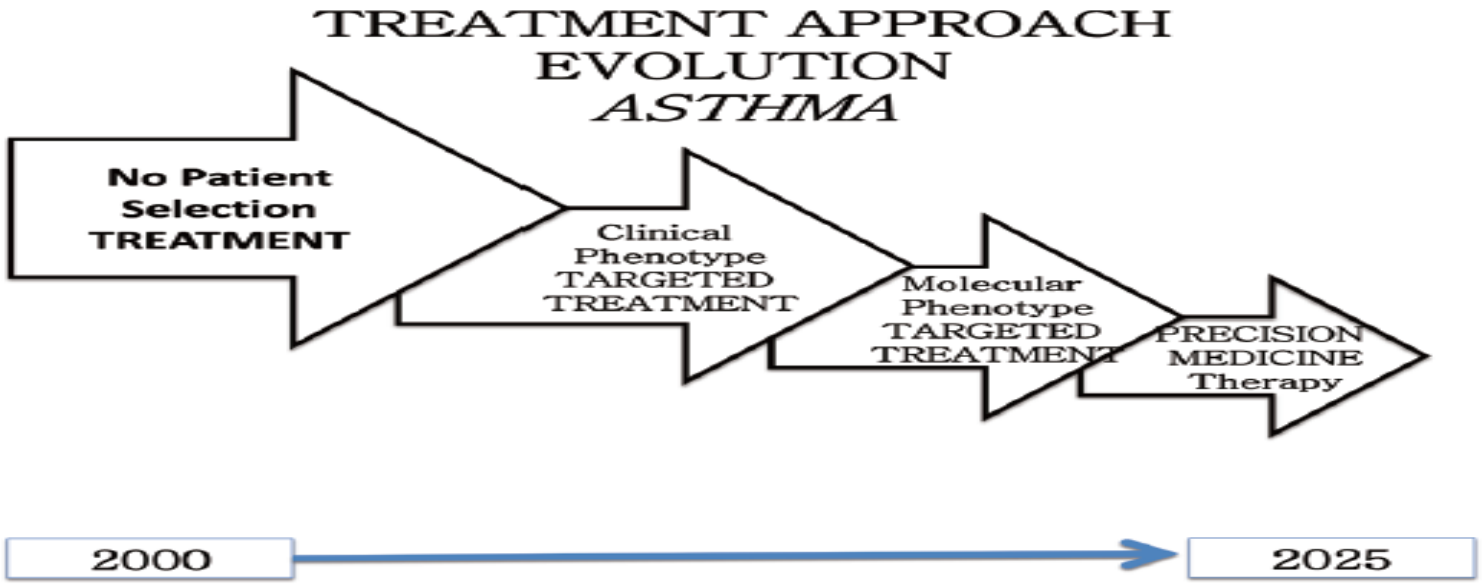


Fig. 1. Evolution of treatment in asthma, from a therapy applicable to any patients to a precision medicine.

Approccio terapeutico

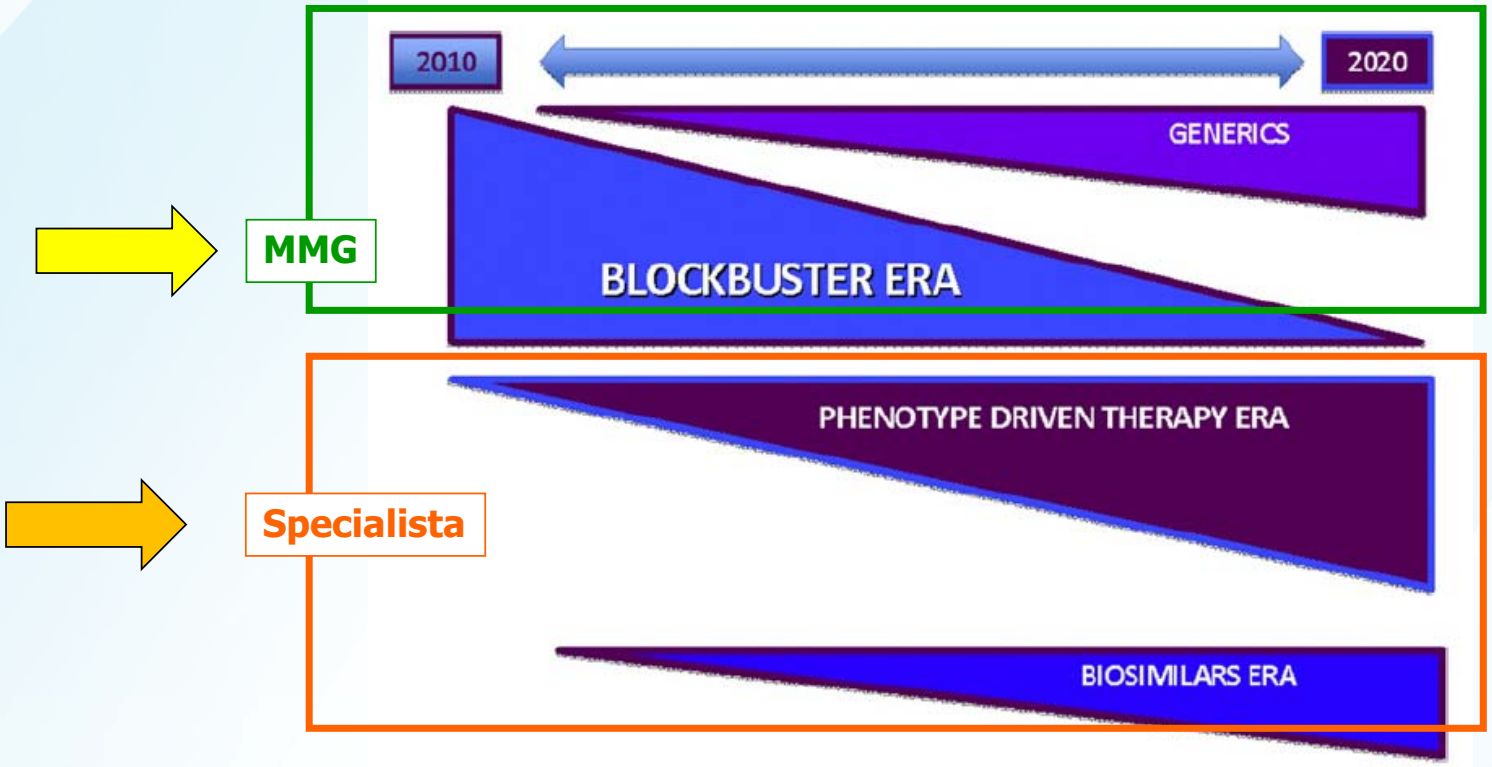
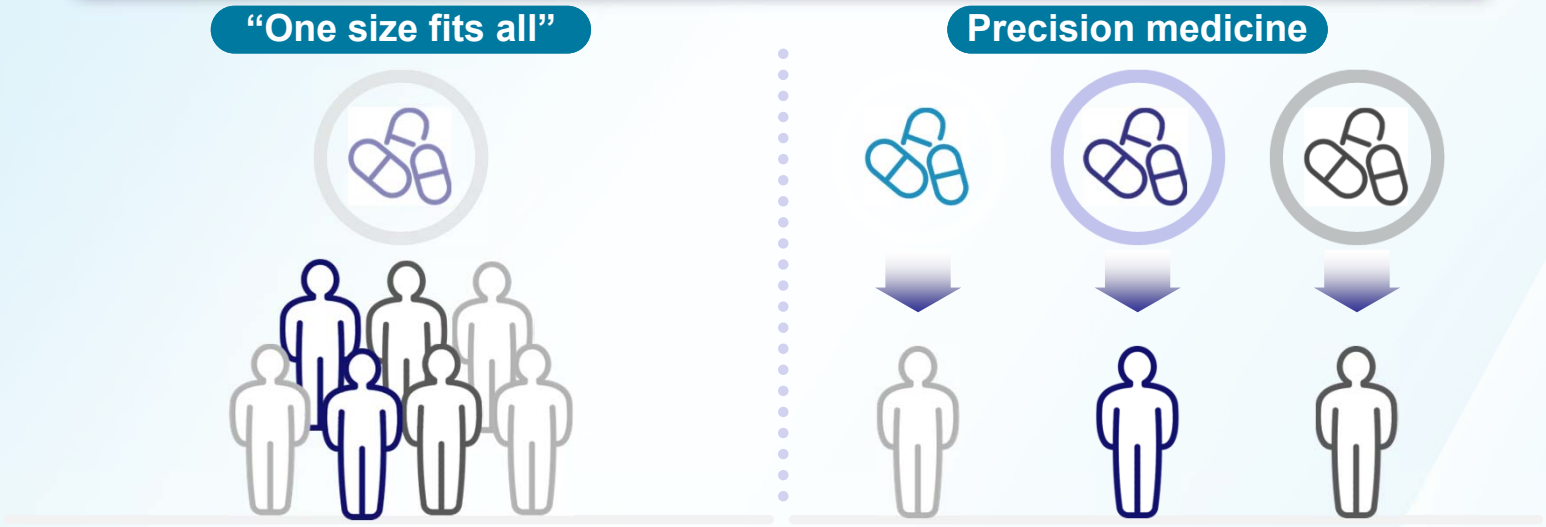


Fig. 1. Future scenario in allergy and asthma treatment.

BRAIDO F. Pulmonary Pharmacology & Therapeutics 25 (2012) 483-486

Precision Medicine Has Been Proposed for the Management of Patients With Severe Asthma[1]

Due to the heterogenous nature of severe asthma,* there may be a need for precision medicine to aid in the selection of a more targeted treatment option



*Severe asthma characterized by the inability to achieve adequate control with high-dose inhaled corticosteroids (ICS) and additional controllers or by oral corticosteroid (OCS) treatment, or is lost when treatment is reduced.

1. Papaioannou AI, et al. *Respir Med*. 2018;142:15-22.

TERAPIA PERSONALIZZATA: PAZIENTE AL CENTRO

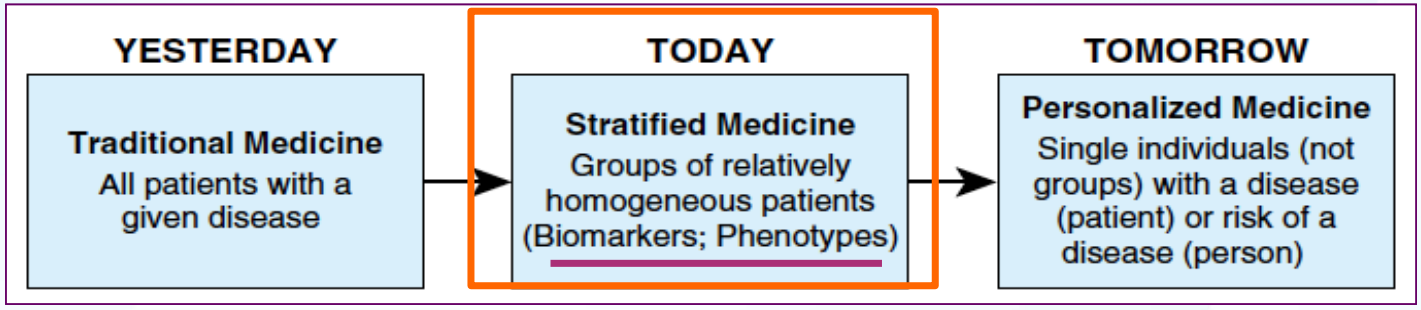
Asthma: a complex syndrome of many diseases?

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.

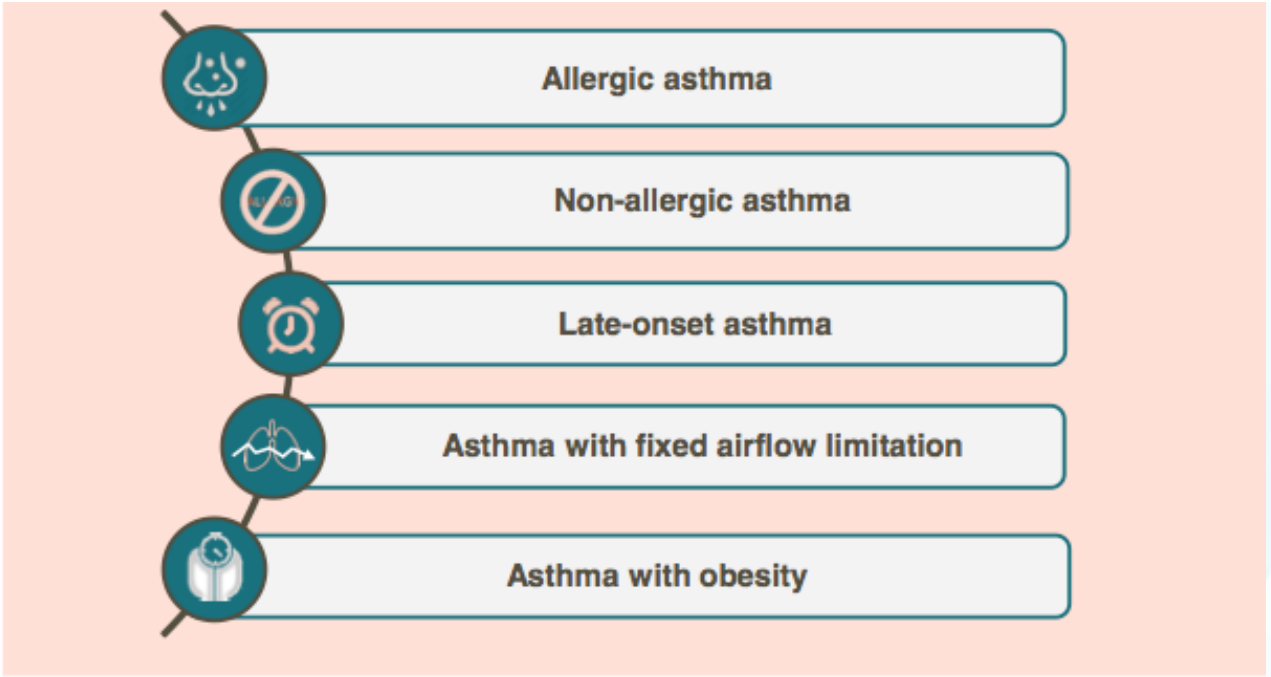
Asthma phenotypes

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'.[5-7] In patients with more severe asthma, some phenotype-guided treatments are available. However, to date, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses.[8] More research is needed to understand the clinical utility of phenotypic classification in asthma.



(GINA 2018)

Phenotypes according to GINA

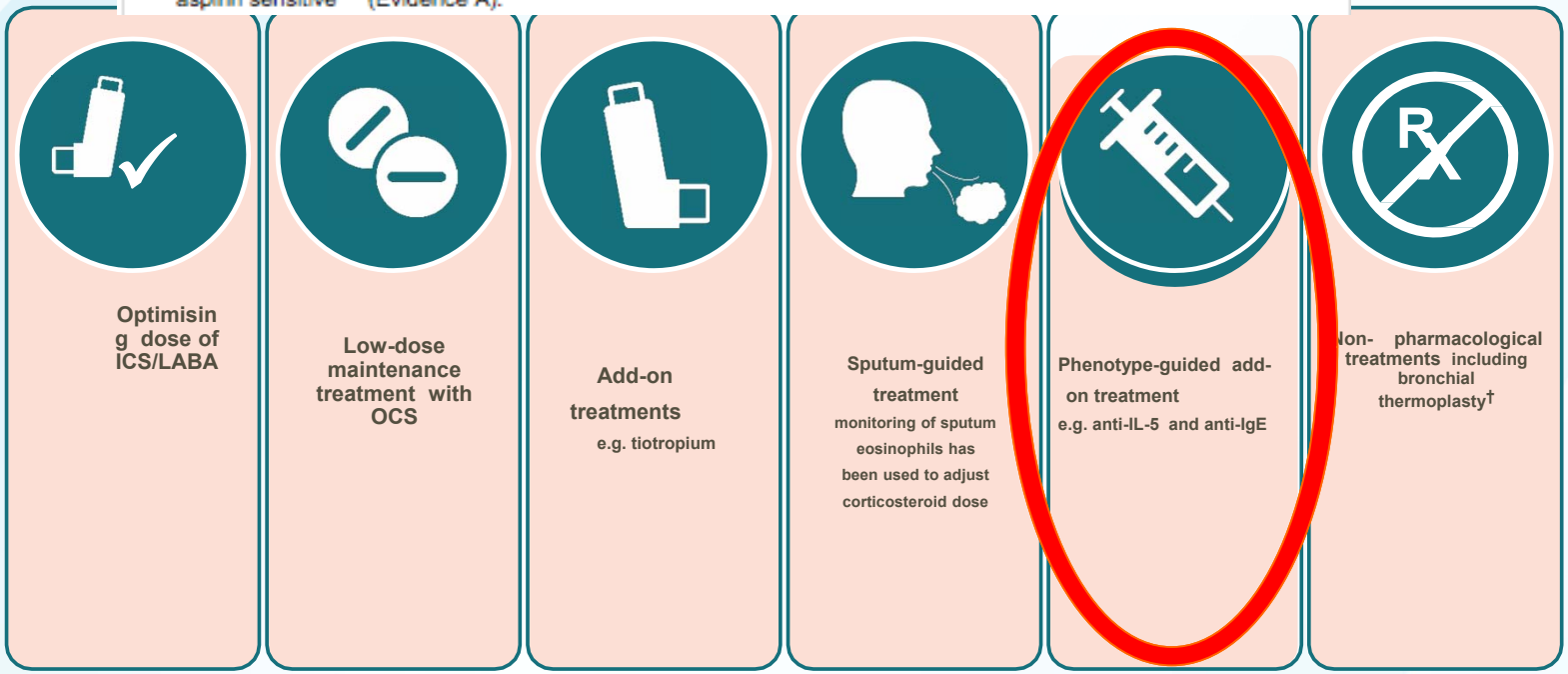


Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2016. Available from: https://www.ginasthma.org

Management of severe asthma: Step 5 GINA

ICS are the therapeutic mainstay for the treatment of severe asthma

- **Phenotype-guided add-on treatment**: patients with severe asthma, uncontrolled on Step 4 treatment, may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[6,7,148,355] Patients ≥6 years with severe allergic asthma with elevated IgE levels may benefit from add-on omalizumab (anti-IgE) therapy[207,208] (Evidence A), those with severe eosinophilic asthma may benefit from add-on anti-IL5 therapy (subcutaneous mepolizumab ≥12 years; intravenous reslizumab ≥18 years) or anti-IL5 receptor therapy (subcutaneous benralizumab ≥12 years)[363] (Evidence A), and add-on LTRAs may be helpful for patients found to be aspirin sensitive[352] (Evidence A).



†Evidence is limited and in selected patients. High-altitude treatment or psychological interventions may be helpful in patients with severe asthma; however, the place of these therapies and strategies in severe asthma has not been established.

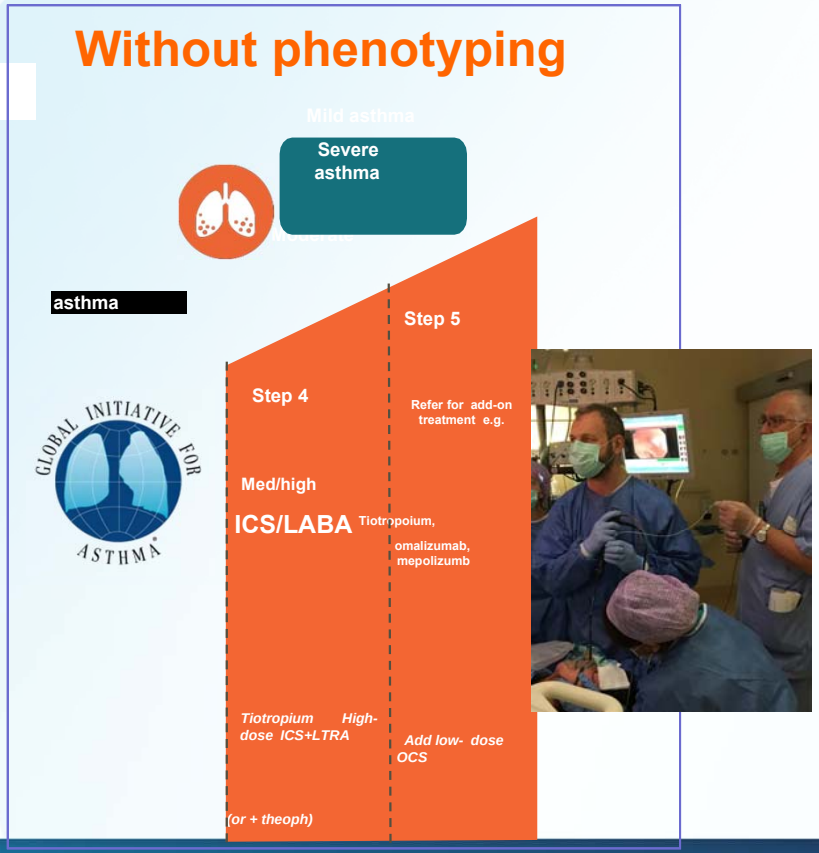
ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β-agonist; OCS, oral corticosteroids

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2016. Available from: https://www.ginasthma.org.

Cluster analyses (*Identifying severe asthma phenotypes)*

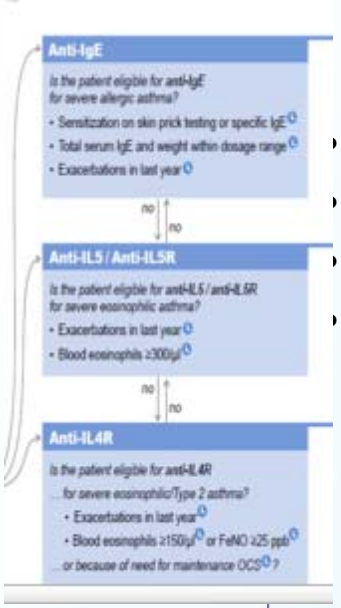
Phenotype directed treatment in severe asthma

Without phenotyping



2020

With phenotyping



- Omalizumab
- Mepolizumab
- Benralizumab
- Dupilumab

Potential phenotypes and endotype in asthma

Clinically defined and responsiveness to therapy

- Defined by severity: mild, moderate, severe
- Characterized by exacerbations
- Early-onset extrinsic asthma
- Late-onset intrinsic asthma
- Corticosteroid-resistant asthma

Defined by triggers and inducers and by association

- Exercise induced
- Aspirin or nonsteroidal induced
- Allergen induced
- Occupational asthma
- Obesity associated
- Cigarette-smoking asthmatic
- Viral induced

Inflammatory endotype

- Eosinophilic
- Neutrophilic

Chung KF, *et al. Ann Am Thorac Soc.* 2013; 10: S109-S117.

Story of severe asthma phenotypes

Asthma Phenotypes: Severe asthma

Studies: SARP, ENFUMOSA, BIOAIR, U BIOPRED, ADEPT

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

Wendy C. Moore[1,2], Deborah A. Meyers[1,2], Sally E. Wenzel[2], W. Gerald Teague[2], Huashi Li[1], Xingnan Li[1], Ralph D'Agostino, Jr.[3], Mario Castro[2], Douglas Curran-Everett[2], Anne M. Fitzpatrick[2], Benjamin Gaston[2], Nizar N. Jarjour[2], Ronald Sorkness[2], William J. Calhoun[2], Kian Fan Chung[2], Suzy A. A. Comhair[2], Raed A. Dweik[2], Elliot Israel[2], Stephen P. Peters[1,2], William W. Busse[2], Serpil C. Erzurum[2], and Eugene R. Bleecker[1,2], for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program[2*]

[1]Wake Forest University School of Medicine, Center for Human Genomics; [2]The Severe Asthma Research Program, Bethesda, Maryland; and [3]Wake Forest University School of Medicine, Public Health Sciences, Winston-Salem, North Carolina

Silkoff et al. Respiratory Research (2015) 16:142
DOI 10.1186/s12931-015-0299-y

RESPIRATORY RESEARCH

RESEARCH Open Access

Asthma characteristics and biomarkers from the Airways Disease Endotyping for Personalized Therapeutics (ADEPT) longitudinal profiling study

P. E. Silkoff[1*], I. Strambu[2], M. Laviolette[3], D. Singh[4], J. M. FitzGerald[5,6], S. Lam[5,6], S. Kelsen[7], A. Eich[8], A. Ludwig-Sengpiel[9], G. C hupp[10], V. Backer[11], C. Porsbjerg[11], P. O. Girodet[12], P. Berger[12], R. Leigh[13], J. N. Kline[14], M. Dransfield[15], W. Calhoun[16], A. Hussaini[17], S. Khatri[18], P. Chanez[19], V. S. Susulic[1], E. S. Barnathan[1], M. Curran[1], A. M. Das[1], C. Brodmerkel[1], F. Baribaud[1] and M. J. Loza[1]

Eur Respir J 2003; 22: 470–477
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European Respiratory Journal
ISSN 0903-1936

The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma

The ENFUMOSA Study Group*

ORIGINAL ARTICLE
ASTHMA

Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort

Dominick E. Shaw[1,44], Ana R. Sousa[2,44], Stephen J. Fowler[3], Louise J. Fleming[4], Graham Roberts[5,6,7], Julie Corfield[8,9], Ioannis Pandis[10], Aruna T. Bansal[11], Elisabeth H. Bel[12], Charles Auffray[13], Chris H. Compton[2], Hans Bisgaard[14], Enrica Bucchioni[15], Massimo Caruso[16], Pascal Chanez[17], Barbro Dahlén[18], Sven-Erik Dahlen[19], Kerry Dyson[20], Urs Frey[21], Thomas Geiser[22], Maria Gerhardsson de Verdier[8], David Gibeon[4], Yi-ke Guo[10], Simone Hashimoto[12], Gunilla Hedlin[23], Elizabeth Jeyasingham[24], Pieter-Paul W. Hekking[12], Tim Higenbottam[25], Ildikó Horváth[26], Alan J. Knox[1], Norbert Krug[27], Veit J. Erpenbeck[28], Lars X. Larsson[8], Nikos Lazarinis[18], John G. Matthews[29], Roelinde Middelveld[30], Paolo Montuschi[30], Jacek Musial[31], David Myles[32], Laurie Pahus[33], Thomas Sandström[34], Wolfgang Seibold[35], Florian Singer[36], Karin Strandberg[18], Jorgen Vestbo[37], Nadja Vissing[38], Christophe von Garnier[22,39], Ian M. Adcock[4,40], Scott Wagers[41], Anthony Rowe[42], Peter Howarth[43], Ariane H. Wagener[12], Ratko Djukanovic[43], Peter J. Sterk[12,45] and Kian Fan Chung[4,40,45]

TRANSATLANTIC AIRWAY CONFERENCE

Clinical Heterogeneity in the Severe Asthma Research Program

Wendy C. Moore[1], Anne M. Fitzpatrick[2], Xingnan Li[1], Annette T. Hastie[1], Huashi Li[1], Deborah A. Meyers[1], and Eugene R. Bleecker[1]

[1]Wake Forest University School of Medicine, Center for Human Genomics, Winston Salem, North Carolina; and [2]Emory University School of Medicine, Atlanta, Georgia

Review | Journal of INTERNAL MEDICINE

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doi: 10.1111/j.1365-2796.2012.02558.x

US and European severe asthma cohorts: what can they teach us about severe asthma?

M. Kupczyk[1,3] & S. Wenzel[2]

Table 6 *Clinical characteristics of the severe asthma cohorts as compared with mild-to-moderate asthmatics in SARP, ENFUMOSA and BIOAIR networks*

Variable	SARP	ENFUMOSA	BIOAIR
Age	Older	No difference	Older
Sex	No difference	Females 4 : 1	
BMI	No differen	Fe	
Atopy	Decreased		
Aspirin hypersensitivity	Increased	Inc	
Sinusitis	Increased	Increas females	Not studied
GERD	Increased	Not reported	Not studied

There is a large **heterogeneity** in severe asthma population

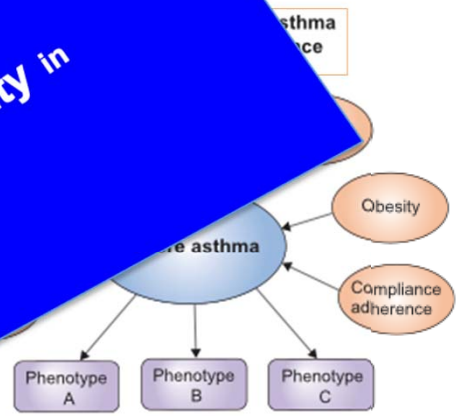
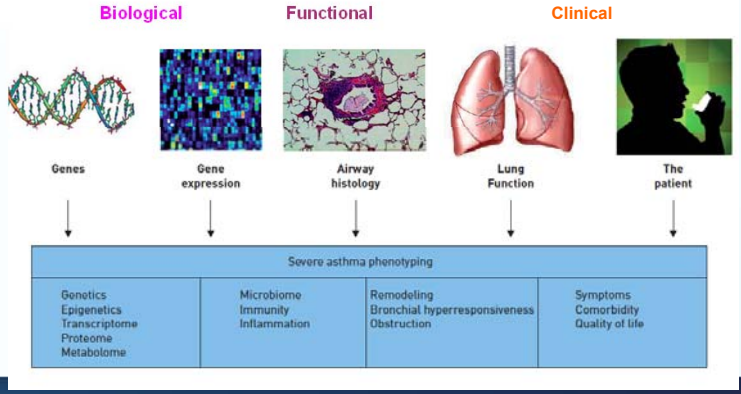


Fig. 1 *Factors influencing severe asthma, development and persistence.*

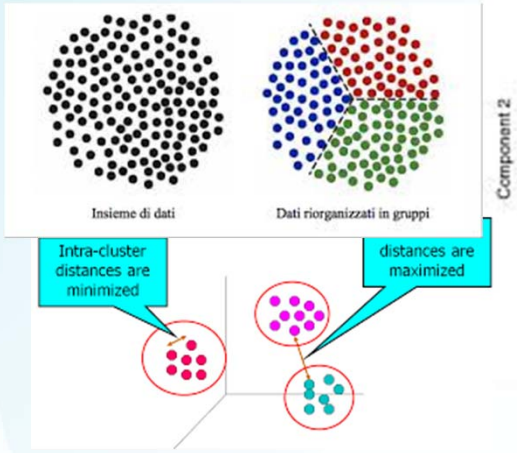


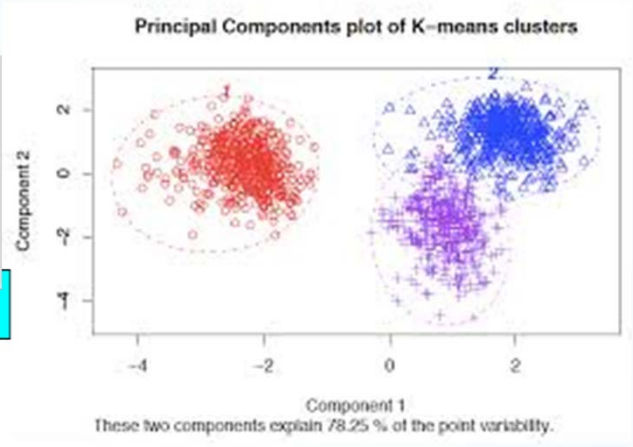
Cluster analyses

Identifying severe asthma phenotypes

What is a cluster analysis?

A mathematical method for exploring data with a view to discovering sub-groups or clusters of homogeneous observations





1. Everitt BS et al. 2011. Cluster Analysis, 5th Edition doi: 10.1002/9780470977811.fmatter; 2. Haldar P et al. *Am J Respir Crit Care Med*. 2008;178:218–224; 3. Moore WC et al. *Am J Respir Crit Care Med.* 2010;181:315–23; 4. Siroux V et al. *Eur Respir J* 2011;38:310–317; 5. Shaw DJ et al. *Eur Respir J*. 2015;46:1308–1321.

Cluster analyses

Identifying severe asthma phenotypes

These studies support the **concept of disease heterogeneity** in asthma and suggest differences in pathophysiologic mechanisms between clusters

- ✓ **Haldar et al**. This study was the first to apply the principles of cluster analysis to distinguishing asthma phenotypes
- ✓ **Moore et al.** the Severe Asthma Research Program
- ✓ **Siroux et al.** an adult asthma population-based study
- ✓ **Shaw et al.** from the Unbiased Biomarkers for the Prediction of Respiratory Disease outcomes project

1. Everitt BS et al. 2011. Cluster Analysis, 5th Edition doi: 10.1002/9780470977811.fmatter; 2. Haldar P et al. *Am J Respir Crit Care Med*. 2008;178:218–224; 3. Moore WC et al. *Am J Respir Crit Care Med.* 2010;181:315–23; 4. Siroux V et al. *Eur Respir J* 2011;38:310–317; 5. Shaw DJ et al. *Eur Respir J*. 2015;46:1308–1321.

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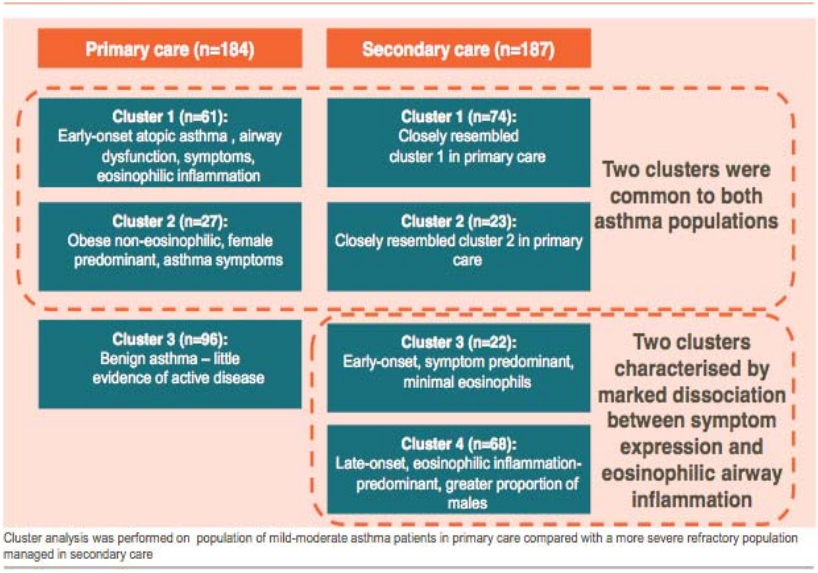
Author Manuscript
Am J Respir Crit Care Med. Author manuscript; available in PMC 2014 April 21.

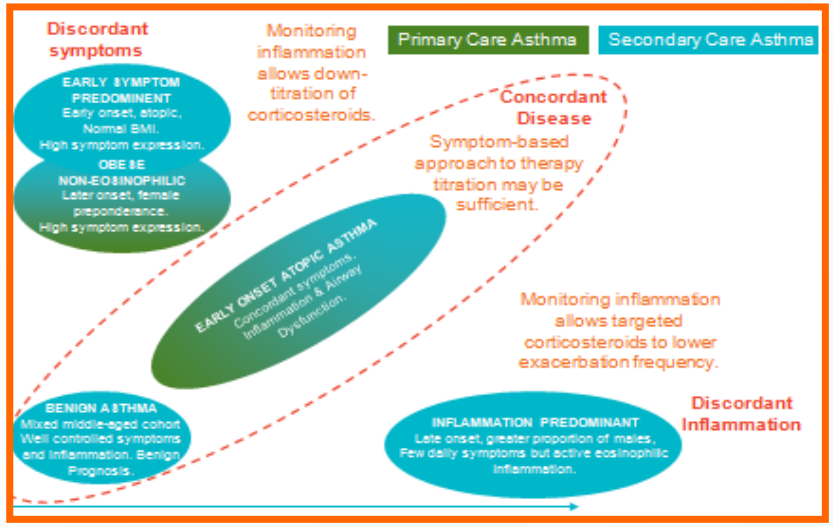
Published in final edited form as:
Am J Respir Crit Care Med. 2008 August 1; 178(3): 218–224. doi:10.1164/rccm.200711-1754OC.

Cluster Analysis and Clinical Asthma Phenotypes

Pranab Haldar[#1], **Ian D. Pavord**[#1], **Dominic E. Shaw**[1], **Michael A. Berry**[1], **Michael Thomas**[2], **Christopher E. Brightling**[1], **Andrew J. Wardlaw**[1], and **Ruth H. Green**[#1]



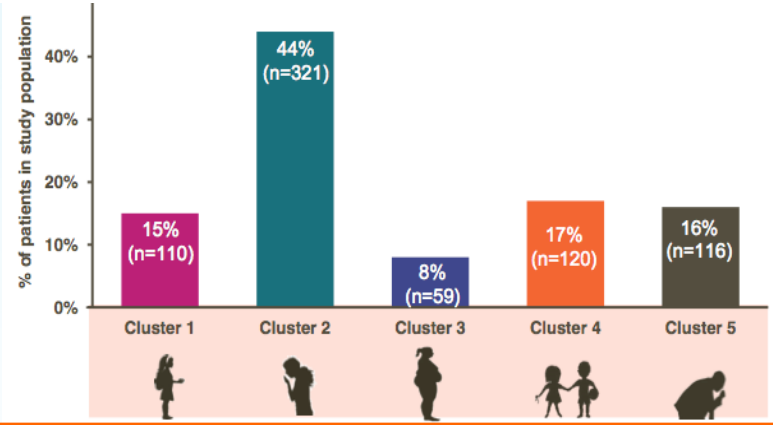
Cluster analysis was performed on population of mild-moderate asthma patients in primary care compared with a more severe refractory population managed in secondary care

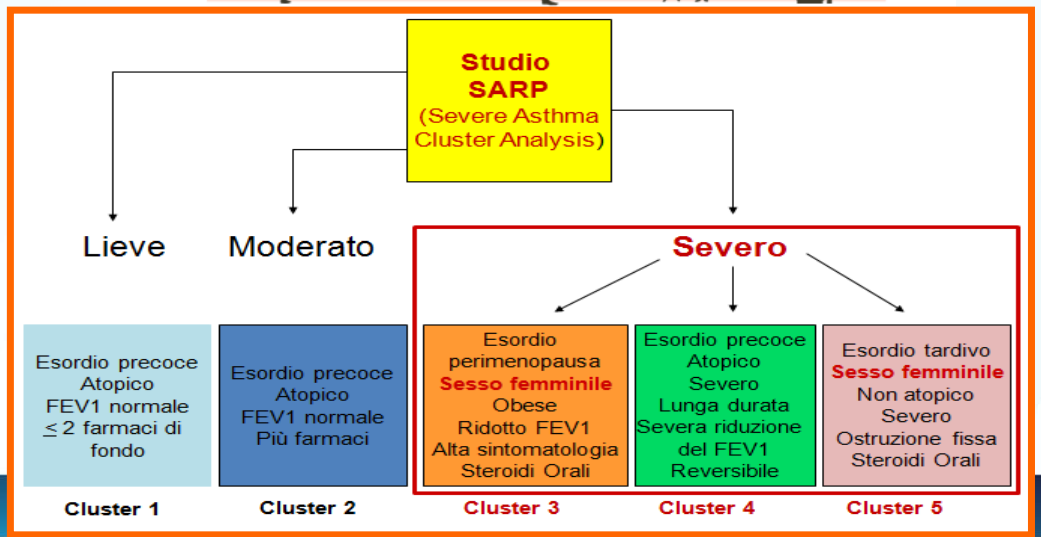


Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

ATS Journals

Wendy C. Moore[1,2], Deborah A. Meyers[1,2], Sally E. Wenzel[2], W. Gerald Teague[2], Huashi Li[1], Xingnan Li[1], Ralph D'Agostino, Jr.[3], Mario Castro[2], Douglas Curran-Everett[2], Anne M. Fitzpatrick[2], Benjamin Gaston[2], Nizar N. Jarjour[2], Ronald Sorkness[2], William J. Calhoun[2], Kian Fan Chung[2], Suzy A. A. Comhair[2], Raed A. Dweik[2], Elliot Israel[2], Stephen P. Peters[1,2], William W. Busse[2], Serpil C. Erzurum[2], and Eugene R. Bleecker[1,2], for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program[2]*





AJRCCM 2010

Eur Respir J 2011; 38: 310–317
DOI: 10.1183/09031936.00120810
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Identifying adult asthma phenotypes using a clustering approach

V. Siroux*,#, X. Basagaña¶,+,§,f, A. Boudier*,#, I. Pin*,#,**, J. Garcia-Aymerich¶,+,§,f, A. Vesin#,##, R. Slama*,#, D. Jarvis¶¶, J.M. Anto¶,+,§,f, F. Kauffmann++,§§ and J. Sunyer¶,+,§,f

Two clinically relevant phenotypes were identified:

- Younger subjects
- Early disease onset
- Allergy
- Active disease at time of examination

Active-treated allergic childhood-onset asthma

- Older subjects
- Predominantly female
- Late disease onset
- Active disease at time of examination
- Highly symptomatic
- Frequent exacerbations

Active-treated adult-onset asthma

40

Siroux V et al. *Eur Respir J.* 2011;38:310–317.

latent class analysis

+

Two phenotypes of subjects with inactive or mild untreated asthma

ORIGINAL ARTICLE
ASTHMA

Eur Respir J 2015; 46: 1308–1321 | DOI: 10.1183/13993003.00779-2015

Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort

Dominick E. Shaw[1,44], Ana R. Sousa[2,44], Stephen J. Fowler[3], Louise J. Fleming[4], Graham Roberts[5,6,7],

- The U-BIOPRED study aimed to improve the understanding of asthma using a systems biology approach
- It was a prospective multicentre study that included patients with severe asthma, patients with mild-to-moderate asthma and healthy controls
- Patients grouped according to asthma severity and smoking status versus healthy non-smoking controls (N=611)

The Predefined adult asthma group cluster end characteristics were:

Severe non-smoking	Smoking and ex-smoking with severe asthma	Mild-to-moderate non-smoking
• Predominantly female, higher ICU admission rates versus other groups, high BMI, nasal polyps and GERD prevalent, low mucolytic usage	• Late-onset, high BMI, nasal polyp and GERD prevalent, low SABA and antihistamine usage	• High positive allergy testing, asthma generally well controlled while receiving low-dose ICS, with low ICU admission rates and low comorbidity prevalence

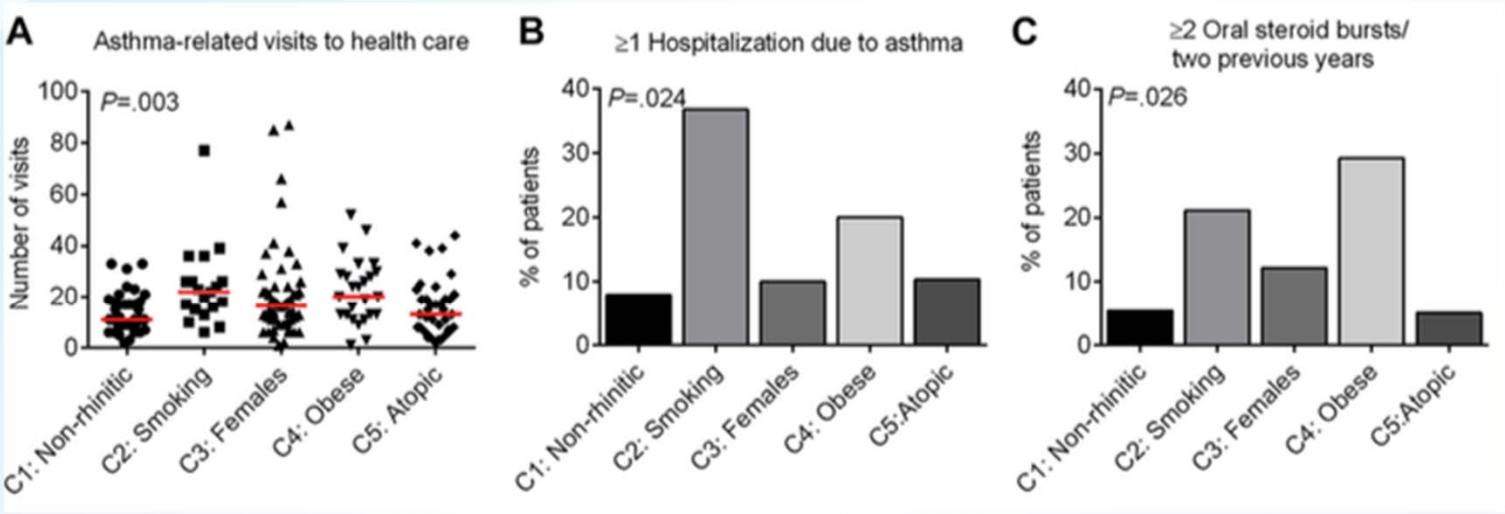
Patients grouped according to asthma severity and smoking status versus healthy; Analysed by symptoms, quality of life, asthma control, allergic status and genotype over 12–14 months

41

Shaw DJ et al. *Eur Respir J*. 2015;46:1308–1321.

Original Article

Cluster Analysis on Longitudinal Data of Patients with Adult-Onset Asthma



- **This cohort included smokers and patients with comorbidities phenotypes based on 12-year follow-up data.**
- **The adult onset asthma is more heterogeneous with compared with childhood-onset asthma**

Illmarinen P J Allergy Clin Immunol Pract 2017

Asthma phenotypes

Genetic heterogeneity of asthma phenotypes identified by a clustering approach

Valérie Siroux[1,2,23], Juan R. González[3,4,5,23], Emmanuelle Bouzigon[6,7], Ivan Curjuric[8,9], Anne Boudier[1,2], Medea Imboden[8,9], Josep Maria Anto[3,5,10,11], Ivo Gut[12,13], Deborah Jarvis[14], Mark Lathrop[7,12], Ernst Reidar Omenaas[15,16], Isabelle Pin[1,2,17], Mathias Wjst[18,19], Florence Demenais[6,7], Nicole Probst-Hensch[8,9], Manolis Kogevinas[3,5,11,20] and Francine Kauffmann[21,22]

Eur Respir J 2014; 43: 439–452 | DOI: 10.1183/09031936.00032713

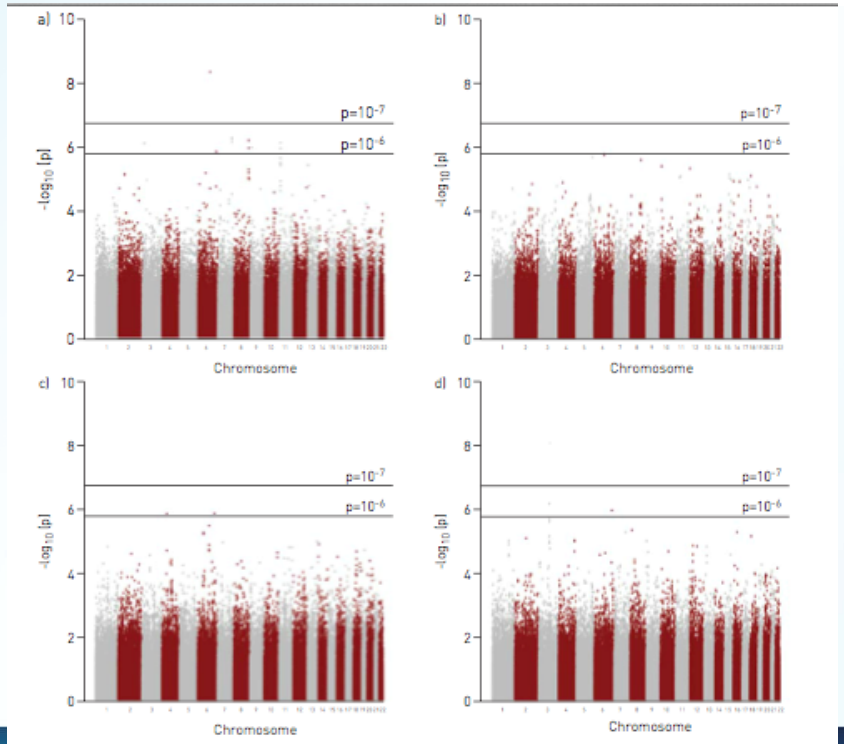


FIGURE 2 Manhattan plots of association results for each asthma phenotype. a) Phenotype A, b) phenotype B, c) phenotype C and d) phenotype D.

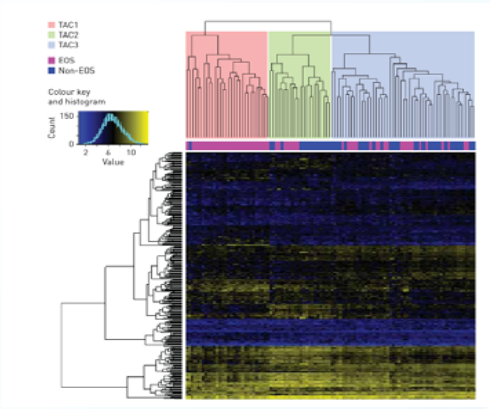
ORIGINAL ARTICLE
ASTHMA

T-helper cell type 2 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in U-BIOPRED

Chih-Hsi Scott Kuo[1,2,3], Stelios Pavlidis[4], Matthew Loza[4], Fred Baribaud[4], Anthony Rowe[4], Ioannis Pandis[3], Ana Sousa[5], Julie Corfield[6,7], Ratko Djukanovic[8], Rene Lutter[9], Peter J. Sterk[9], Charles Auffray[8,10], Yike Guo[3], Ian M. Adcock[1,2,11] and Kian Fan Chung[1,2,11] on behalf of the U-BIOPRED Study Group[12]

Affiliations: [1]Airways Disease, National Heart and Lung Institute, Imperial College London, London, UK. [2]Biomedical Research Unit, Royal Brompton and Harefield NHS Trust, London, UK. [3]Dept of Computing and Data Science Institute, Imperial College London, London, UK. [4]Janssen R&D, High Wycombe, UK. [5]Respiratory Therapeutic Unit, GSK, Stockley Park, UK. [6]AstraZeneca R&D, Mölndal, Sweden. [7]Aretheva R&D, Nottingham, UK. [8]Faculty of Medicine, Southampton University, Southampton, UK. [9]Faculty of Medicine, University of Amsterdam, Amsterdam, The Netherlands. [10]European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL, Université de Lyon, Lyon, France. [11]These authors contributed equally to this work. [12]A full list of the U-BIOPRED Consortium project team member and their affiliations can be found in the Acknowledgements section.

Correspondence: K.F. Chung, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London SW3 6LY, UK. E-mail: f.chung@imperial.ac.uk



SINTOMI

RIACUTIZZAZIONI

FEV1

INFIAMMAZIONE TH2-LIKE

-ASMA SEVERO
-OSTRUZIONE DEL FLUSSO
-POLIPI NASALI
-USO OCS ALTE DOSI
- INSENSIBILITA AI CORTICOSTEROIDI
- ALTA EOSINOFILIA

TAC1

SEVERA EOSINOFILIA

-INFEZIONE BATTERICA
-INFLAMMASOMA
-MODERATA OSTRUZIONE AL FLUSSO
-ECZEMA
-
NEUTROFILIA/EOSINOFILIA

TAC2

SEVERA NEUTROFILIA

INFIAMMAZIONE NON TH2

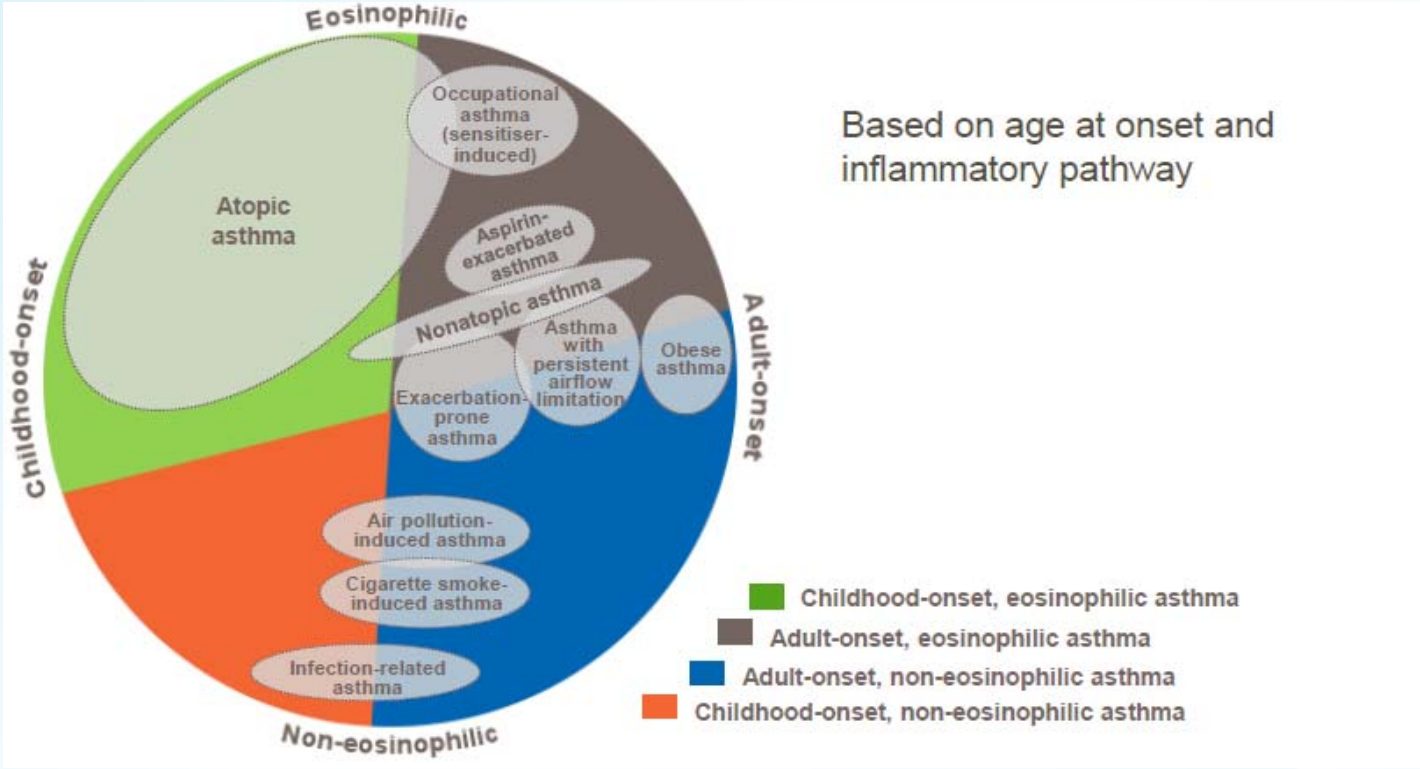
-STRESS OSSIDATIVO/ INVECCHIAMENTO
-MENO RIACUTIZZAZIONI
-LIEVE OSTRUZIONE
-GRANULOCITOPENIA / EOSINIFILIA

TAC3

SEVERA GRANULOCITOPENIA

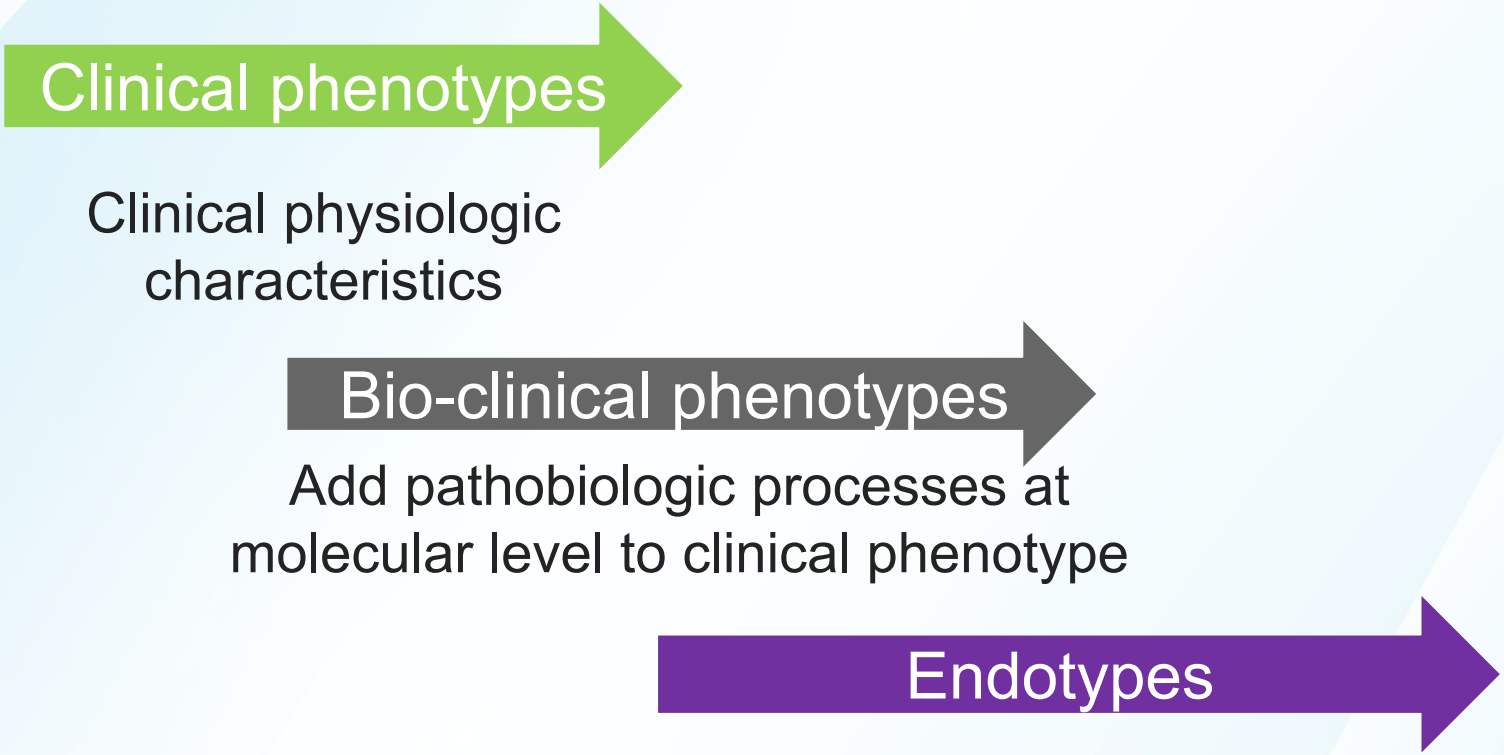
What happens in our clinical practice?

Current understanding of phenotypes in asthma



Hekking PP, *et al. J Allergy Clin Immunol Pract. 2014;*

Transition from Phenotype to Endotype



EUROPEAN RESPIRATORY *journal*

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Early View

Review

Defining severe obstructive lung disease in the biologic era: an endotype-based approach

Richard J. Martin, Elisabeth H. Bel, Ian D. Pavord, David Price, Helen K. Reddel

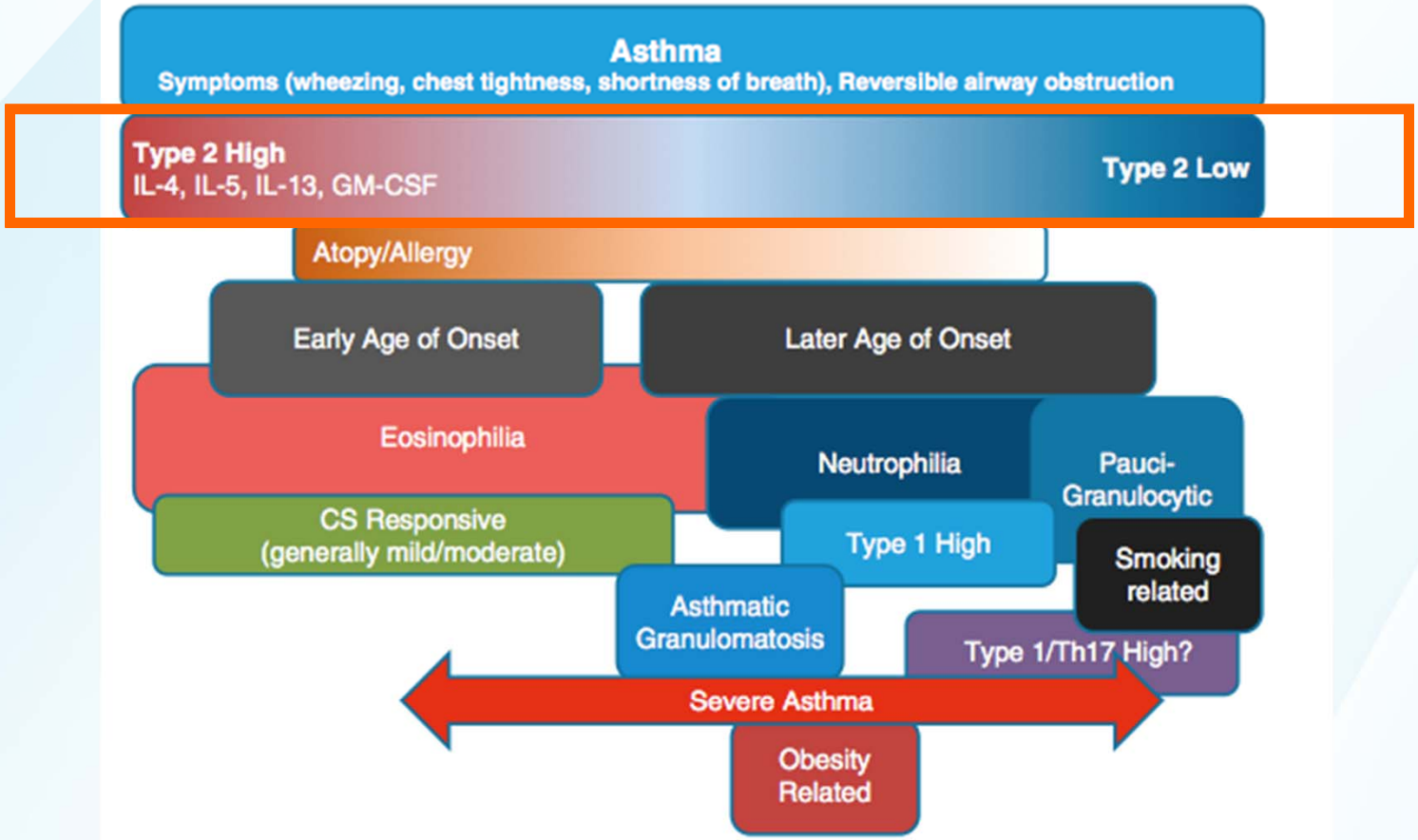
ENDOTIPI

1) Th2 non Th2 (2005)

2) Type 2 high Type 2 low (2015)

3) Tipo 2 Non Tipo 2 (2019)

Evolving Concepts of Asthma



Gauthier, Wenzel AJRCCM 2015

2019 GINA Guidelines Recognize Type 2 Inflammation in the Assessment of Severe Asthma[1]

Characterization of **type 2 inflammation** in the assessment of the severe asthma phenotype

Characterization of patients by **biomarkers of type 2 inflammation**

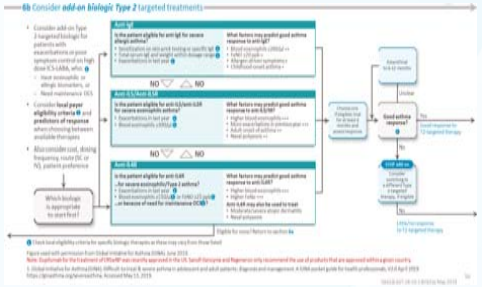
Consideration of add-on **type 2 targeted biologics**

GINA: What Is Type 2 Inflammation?

"**Type 2 inflammation is found in ~50% of people with severe asthma.** It is characterized by cytokines such as **interleukin (IL)-4, IL-5, and IL-13,** which are often produced by the adaptive immune system on recognition of allergens. It may also be activated by viruses, bacteria, and irritants that stimulate the innate immune system via production of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) by epithelial cells. **Type 2 inflammation is often characterized by eosinophils or increased FeNO, and may be accompanied by atopy,** whereas non-Type 2 inflammation is often characterized by neutrophils. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. It may respond to OCS but their serious adverse effects mean that alternative treatments should be sought."

Assess the severe asthma phenotype during high-dose ICS treatment (or lowest possible dose of OCS)

Type 2 inflammation	
Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS
Note: These are **not** the criteria for add-on biologic therapy (see **6b**)	(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)



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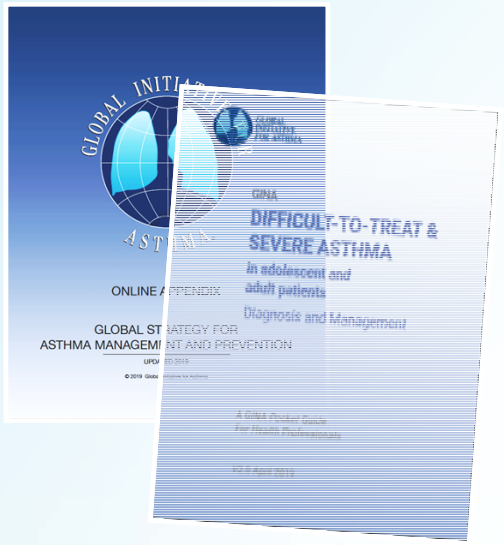
- 1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019.

2019 GINA Guidelines Recognize Type 2 Inflammation in the Assessment of Severe Asthma[1]



What is type 2 inflammation?

- Driven by key cytokines IL-4, IL-5, and IL-13, which result in the inflammatory process[1]
- Found in ~50%-70% of people with severe asthma[1-3]
- often characterized by eosinophils or increased FeNO, and may be accompanied by atopy[1]

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- 1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019. 2. Seys SF, et al. *Respir Res*. 2017;18:39. 3. Peters MC, et al. *J Allergy Clin Immunol*. 2014;133(2):388-394.

2019 GINA Guidelines Recommend Characterization of Patients by Biomarkers of Type 2 Inflammation

Assess the severe asthma phenotype during high-dose ICS treatment (or lowest possible dose of OCS)

2019 GINA Pocket Guide Assessment of Type 2 Inflammation	
Could patient have type 2 airway inflammation? Note: These are **not** the criteria for add-on biologic therapy (see **6b**)	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2% and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

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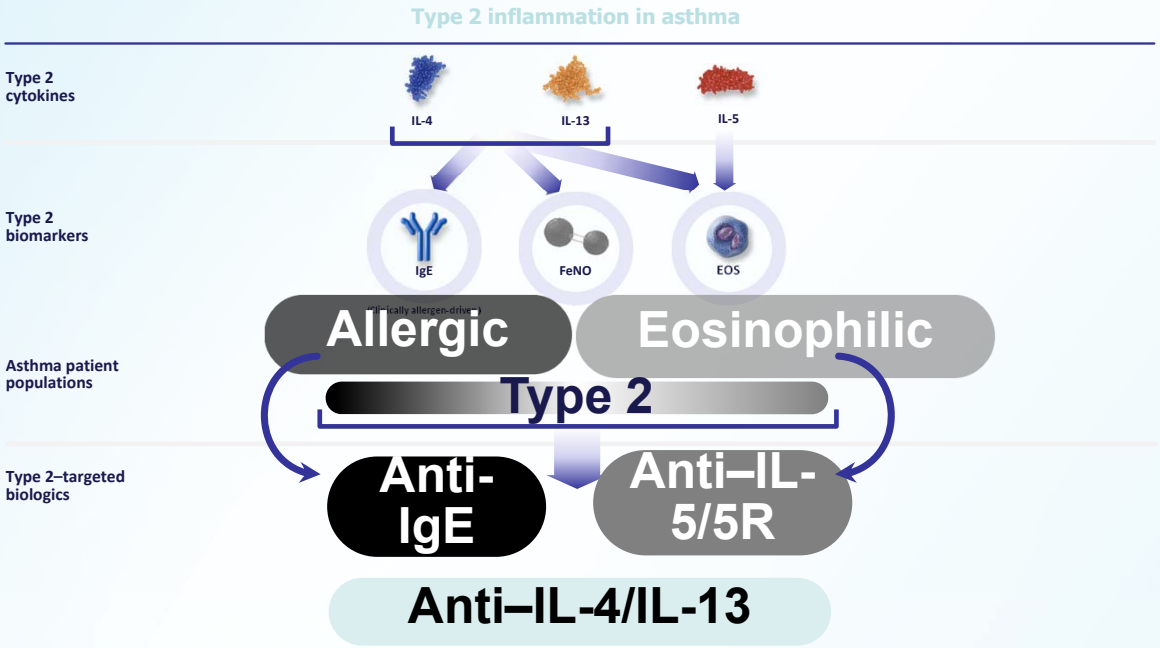
1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019.

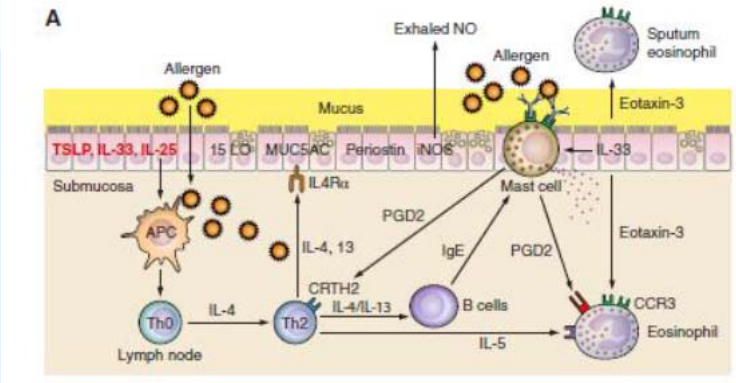
Biologic Therapies Target Key Cytokines and Mediators of Type 2 Inflammation[1-4]

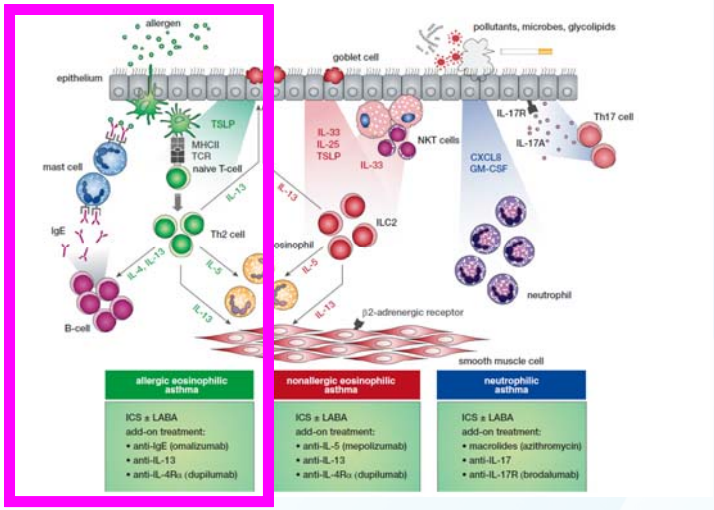


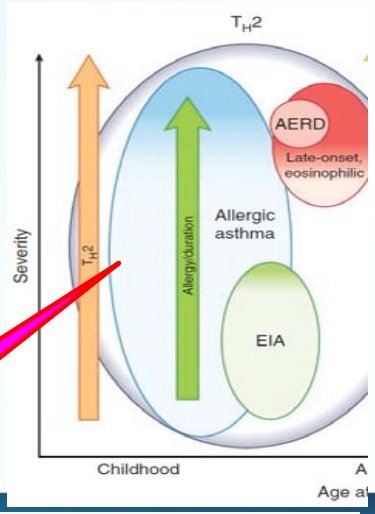
- 1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 2. Katial RK, et al. *J Allergy Clin Immunol Pract*. 2017;5:S1-S14. 3. Robinson D, et al. *Clin Exp Allergy.* 2017;47(2):161-175. 4. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019.

T2 endotype

Early-onset allergic (TH_2) asthma







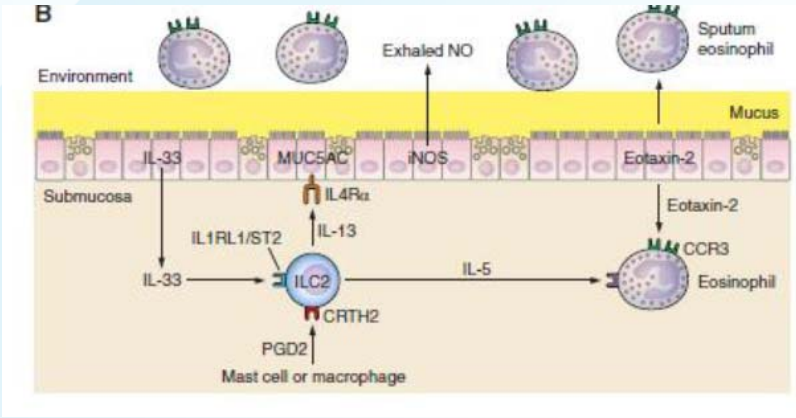
Anti-IgE

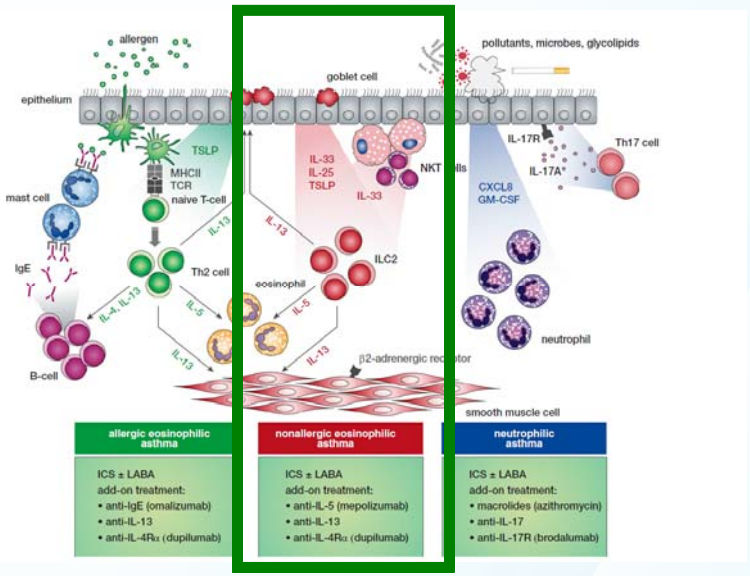
- Early childhood
- Associated with other atopic diseases
- Family history
- Mild to severe (progression?)
- Severity related to the number of IgE sensitivities
- Genes associated are epithelial genes rather than allergy genes
- Higher numbers of TH2 genes products associated with severity
- Biomarkers: FeNO, eosinophils, periostin, IgE?

Ray et al. Am J Physiol Lung Cell Mol Physiol 2015;

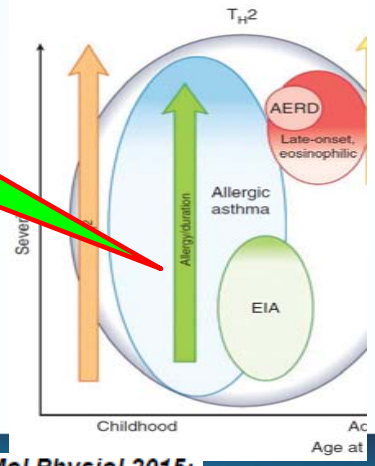
T2 endotype

Late-onset persistent eosinophilic asthma





Anti-IL-5
Anti-IL-4/IL-13



- Late onset
- Severe from the onset
- No clinical allergy
- No family history
- Association with AERD
- Refractoriness to CS
- Biomarkers: IL-5; IL-13;FeNO; periostin, eosinophils (>2% IS, >220/µL blood)

Ray et al. Am J Physiol Lung Cell Mol Physiol 2015;

Biologics for the Treatment of Uncontrolled Persistent Asthma Are Evolving[1-6]

- 1. Xolair (omalizumab) [summary of product characteristics]. Camberly, UK: Novartis Europharm Ltd.; 2019. 2. Nucala (mepolizumab) [summary of product characteristics]. Cork, Ireland: GlaxoSmithKline; 2018. 3. Cinqaero (reslizumab) [summary of product characteristics]. Castleford, UK: Teva Pharmaceuticals Ltd.; 2019. 4. Fasenra (benralizumab) [summary of product characteristics]. Södertälje, Sweden: AstraZeneca AB; 2019. 5. Dupixent (dupilumab) [summary of product characteristics]. Paris, France: sanofi-aventis group; 2019. 6. Regeneron Pharmaceuticals, Inc. Dupixent (dupilumab) approved for severe asthma by European Commission. https://newsroom.regeneron.com/news-releases/news-release-details/dupixentr-dupilumab-approved-severe-asthma-european-commission.
  Accessed December 30, 2019.

ERJ open research

CrossMark click for updates

REVIEW
ASTHMA

Management of the patient with eosinophilic asthma: a new era begins

Jantina C. de Groot[1], Anneke ten Brinke[1] and Elisabeth H.D. Bel[2]

TABLE 1 Clinical profile of late-onset eosinophilic asthma patients

Adult onset of asthma
Equal distribution between sexes
Few or no allergies to common allergens
Elevated eosinophils in peripheral blood
At risk of severe exacerbations
Normal or moderately elevated IgE level
Low FEV_1 and often persistent airflow limitation
Air trapping and dynamic hyperinflation
Chronic rhinosinusitis with nasal polyposis
Aspirin sensitivity
Good response to systemic corticosteroids
Good response to anti IL-5 treatment

Add-On Type 2–Targeted Biologic Therapy May Be Considered for Treatment of Patients With Type 2 Asthma[1]

	Anti-IgE for severe allergic asthma	Anti–IL-5/5R for severe eosinophilic asthma	Anti–IL-4R for severe eosinophilic/type 2 asthma or OCS-dependent severe asthma
Eligibility criteria	• Sensitization on skin prick testing or specific IgE • Total serum IgE and weight within dosage range • Exacerbations in last year	• Exacerbations in last year • Blood eosinophils ≥300/µl	• Exacerbations in last year • Blood eosinophils ≥150/µl or FeNO ≥25 ppb • *OR* need for maintenance OCS
Predictors of good response	• Blood eosinophils ≥260/µl ++ • FeNO ≥20 ppb + • Allergen-driven symptoms + • Childhood-onset asthma +	• Higher blood eosinophils +++ • More exacerbations in previous year +++ • Adult-onset asthma ++ • Nasal polyposis ++	• Higher blood eosinophils +++ • Higher FeNO +++
May also be used to treat	–	–	• Moderate/severe AD • Nasal polyposis

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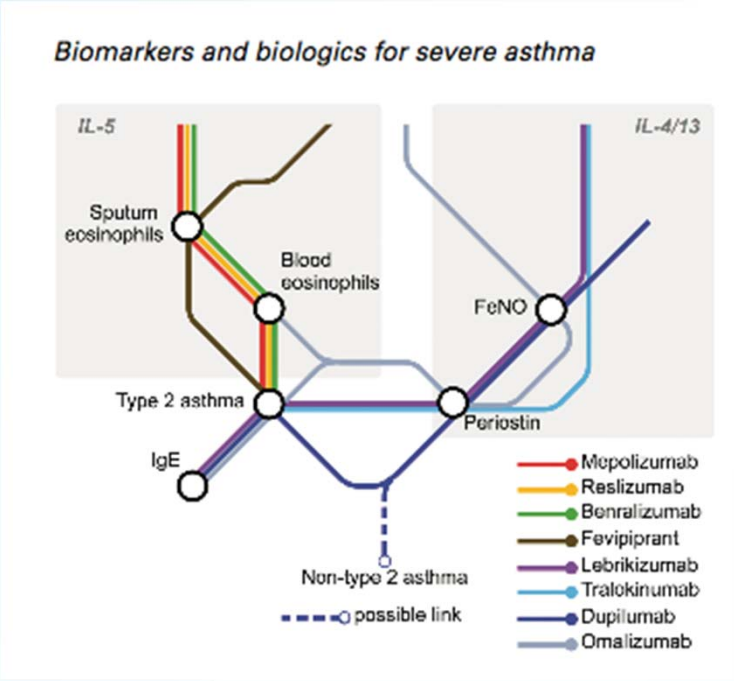
• 1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019.

BIOMARKERS and SEVERE ASTHMA



R Right therapy

R For the Right patient (responder)

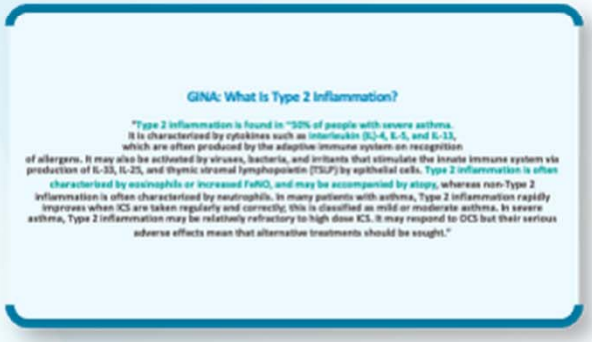
R At the Right time

2019 GINA Guidelines Recognize Type 2 Inflammation in the Assessment of Severe Asthma[1]

Characterization of type 2 inflammation in the assessment of the severe asthma phenotype

Characterization of patients by biomarkers of type 2 inflammation

Consideration of add-on type 2 targeted biologics



Assess the severe asthma phenotype during high-dose ICS treatment (or lowest possible dose of OCS)

Type 2 inflammation

Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS
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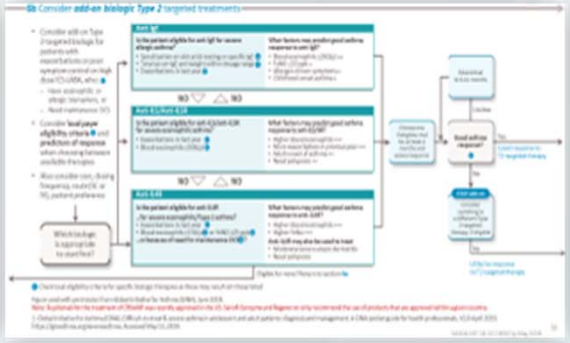

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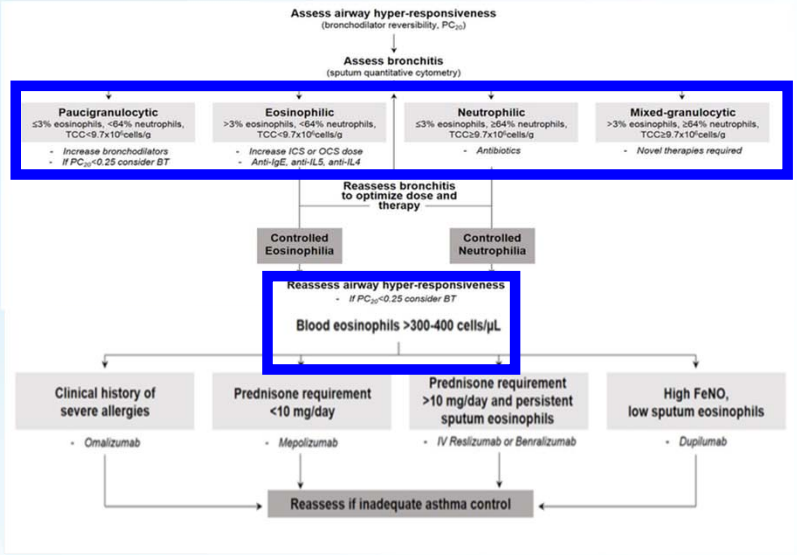
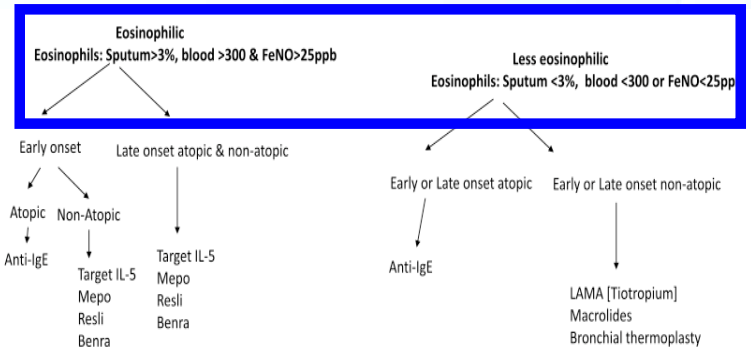
- 1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. https://ginasthma.org/severeasthma. Accessed December 26, 2019.

Asthma Endotypes and an Overview of Targeted Therapy for Asthma

Therapeutic strategy in severe asthma guided by inflammatory endotype and severity of airway hyper-responsiveness



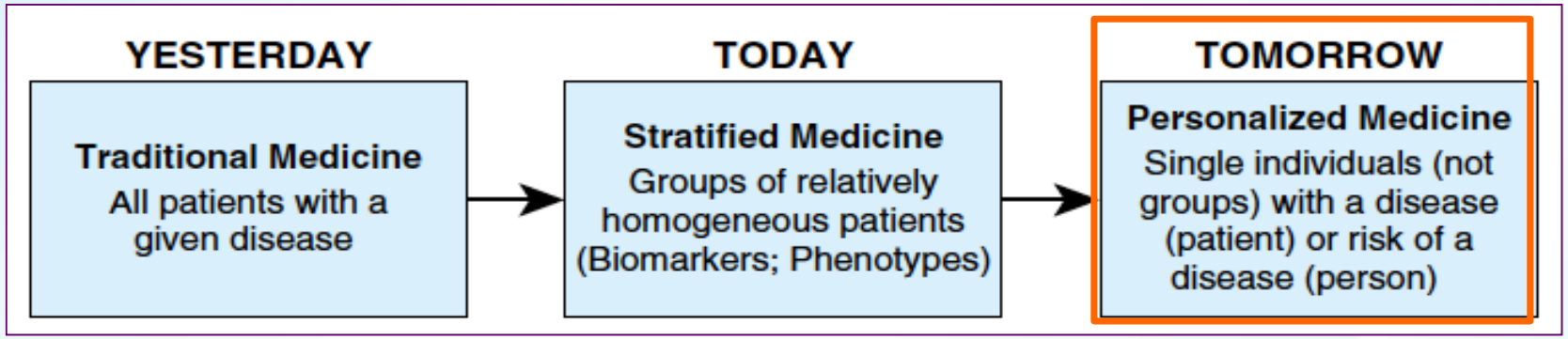
Svenningsen S and Nair P. Front. Med 2017



Personalized Respiratory Medicine: Exploring the Horizon, Addressing the Issues

Summary of a BRN-AJRCCM Workshop Held in Barcelona on June 12, 2014

Alvar Agustí[1,2], Josep Maria Antó[3], Charles Auffray[4], Ferran Barbé[2,5], Esther Barreiro[2,6], Jordi Dorca[2,7], Joan Escarrabill[1], Rosa Faner[1,2], Laura I. Furlong[8], Judith Garcia-Aymerich[3], Joaquim Gea[2,6], Bertil Lindmark[9], Eduard Monsó[2,10], Vicente Plaza[11], Milo A. Puhan[12], Josep Roca[1,2], Juan Ruiz-Manzano[2,13], Laura Sampietro-Colom[1], Ferran Sanz[8], Luis Serrano[14,15], James Sharpe[14,15], Oriol Sibila[11], Edwin K. Silverman[16], Peter J. Sterk[17], and Jacob I. Sznajder[18]



Agusti et al.AJRCCM 2015

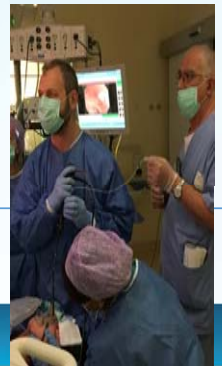
Non T2 endotype

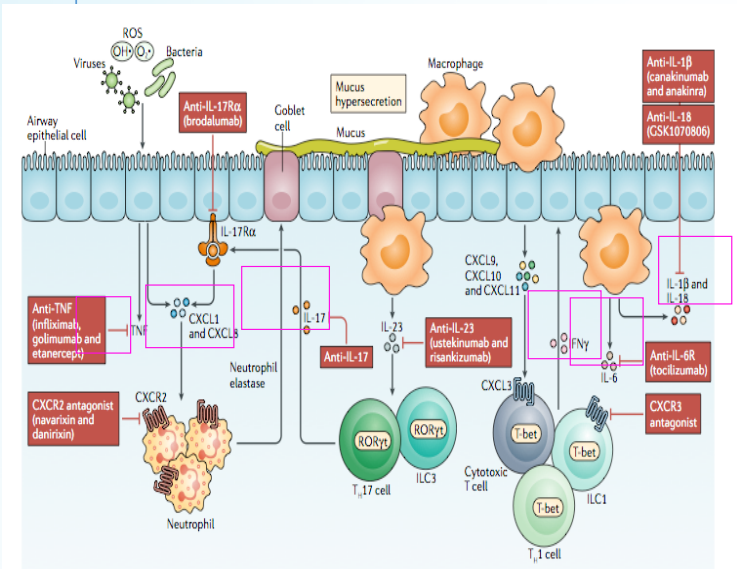
Paucigranulocytic severe asthma

Steroid-insensitive

LAMA
LAMA+LABA
TRIPLE THERAPY?

Bronchial Thermoplasty





Neutrophilic severe asthma

Steroid-insensitive
ANTI-NEUTROPHILIC

None

Macrolide
CXCR2 ant (navarixin)
Anti-IL17RA (brodalumab)
Anti-TNF (infliximab, golimumab, etanercept)
Anti-IL-1β (anakinra)
Anti- IL-6R (tocilizumab)

Approved

Under development

PJ Barnes .Nature reviews 2018

LA CENERENTOLA
Non T2 endotype

GRAZIE PER L'ATTENZIONE