What are the Asthma Phenotypes/Endotypes Relevant for Clinical Practice?

2017년 2월 18일

서울의대 서울특별시보라매병원
호흡기내과 김덕겸

1부 Phenotype in Airway Disease 좌장 : 인광호

14 : 00 ~ 14 : 30 What Are the COPD Phenotypes/Endotypes Relevant for Clinical Practice?
김유일(전남의대 내과)

14 : 30 ~ 15 : 00 What Are the Asthma Phenotypes/Endotypes Relevant for Clinical Practice?
김덕겸(서울의대 내과)

15 : 00 ~ 15 : 30 **Severe Asthma:** Lessons Leamed from Global Studies
허규영(고려의대 내과)

15 : 30 ~ 15 : 50 Coffee Break

2부 Update of Airway Disease 좌장 : 안중현

15 : 50 ~ 16 : 20 In What Patients Should I Use Fixed LABA-LAMA Combination in COPD ?
엄수정(동아의대 내과)

16 : 20 ~ 16 : 50 In What Patients Should I Use LAMA in Asthma ?
박혜윤(성균관의대 내과)

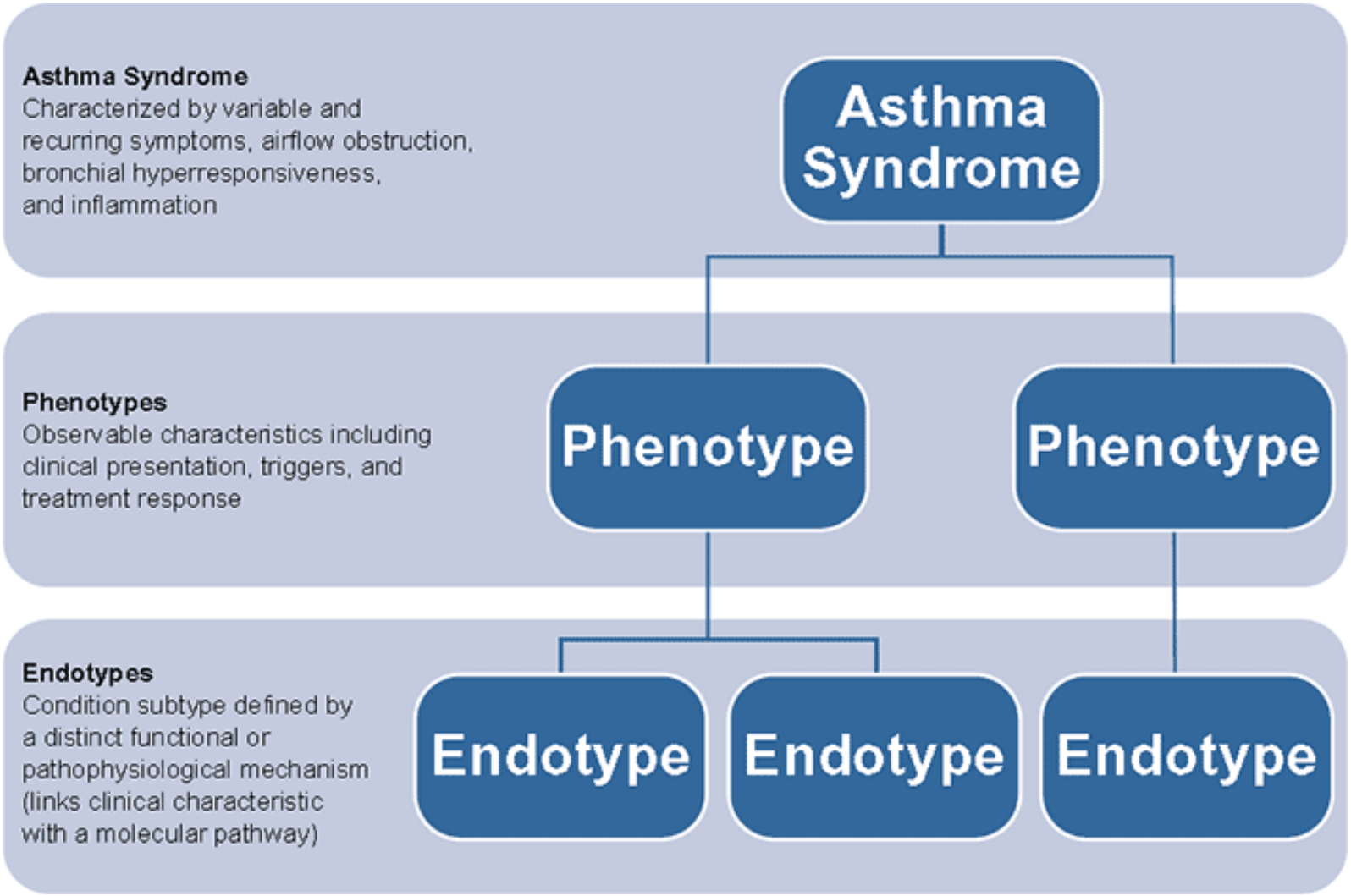
16 : 50 ~ 17 : 20 Update GOLD 2017
정지예(연세의대 내과)

17 : 20 ~ 17 : 30 폐 회 사 안중현 COPD연구회장

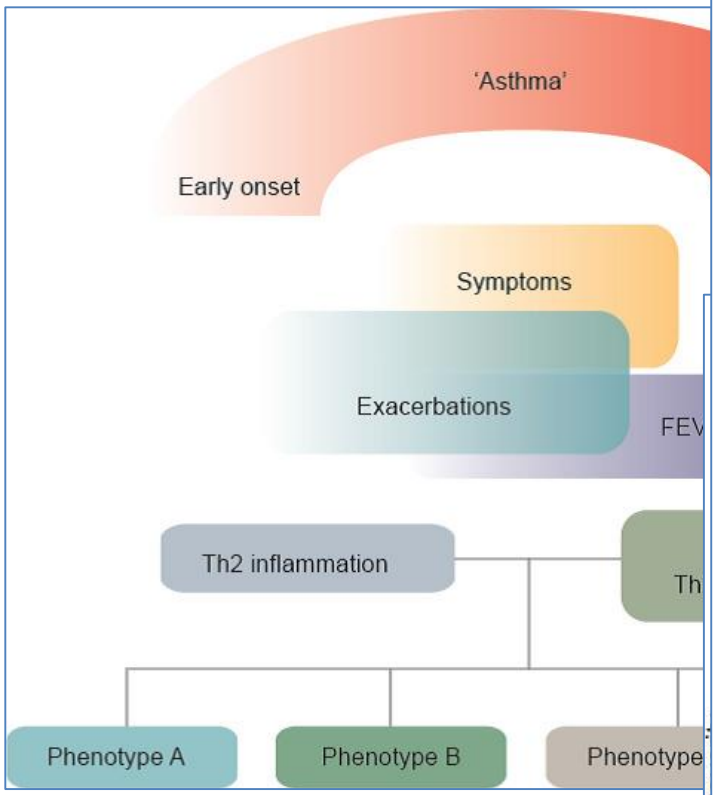
Overview

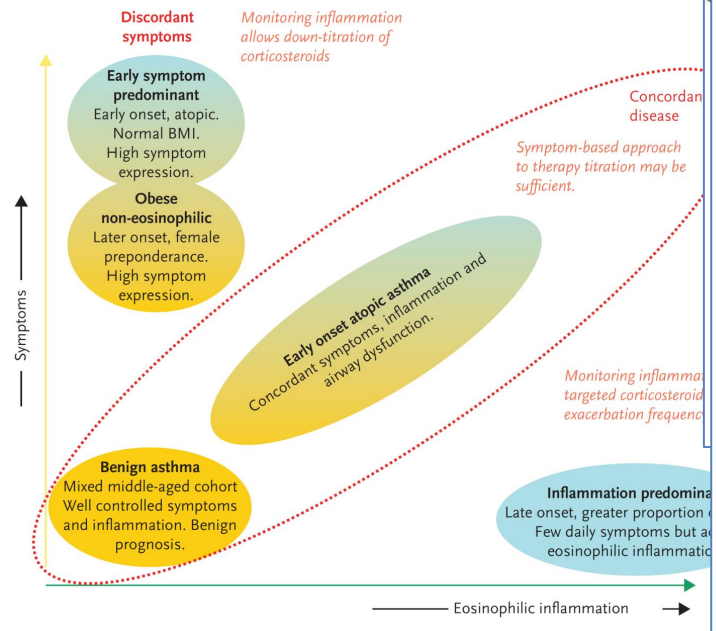
- Asthma phenotyping/endotyping
  - Rationale/background
  - Considerations in applying phenotypes to clinical practice
- What are phenotype/endotypes relevant for clinical practice?
  - Symptom based approach to treatment titration
    - Severe asthma
      - requiring new therapeutic agents
      - biomarker based treatment
  - Phenotypes requiring additional consideration in diagnosis and treatment
      - Smoking and asthma
      - Asthma in Elderly
      - Asthma in Workplace including occupational asthma
      - Aspirin Exacerbated Respiratory Disease (AERD)
- Summary

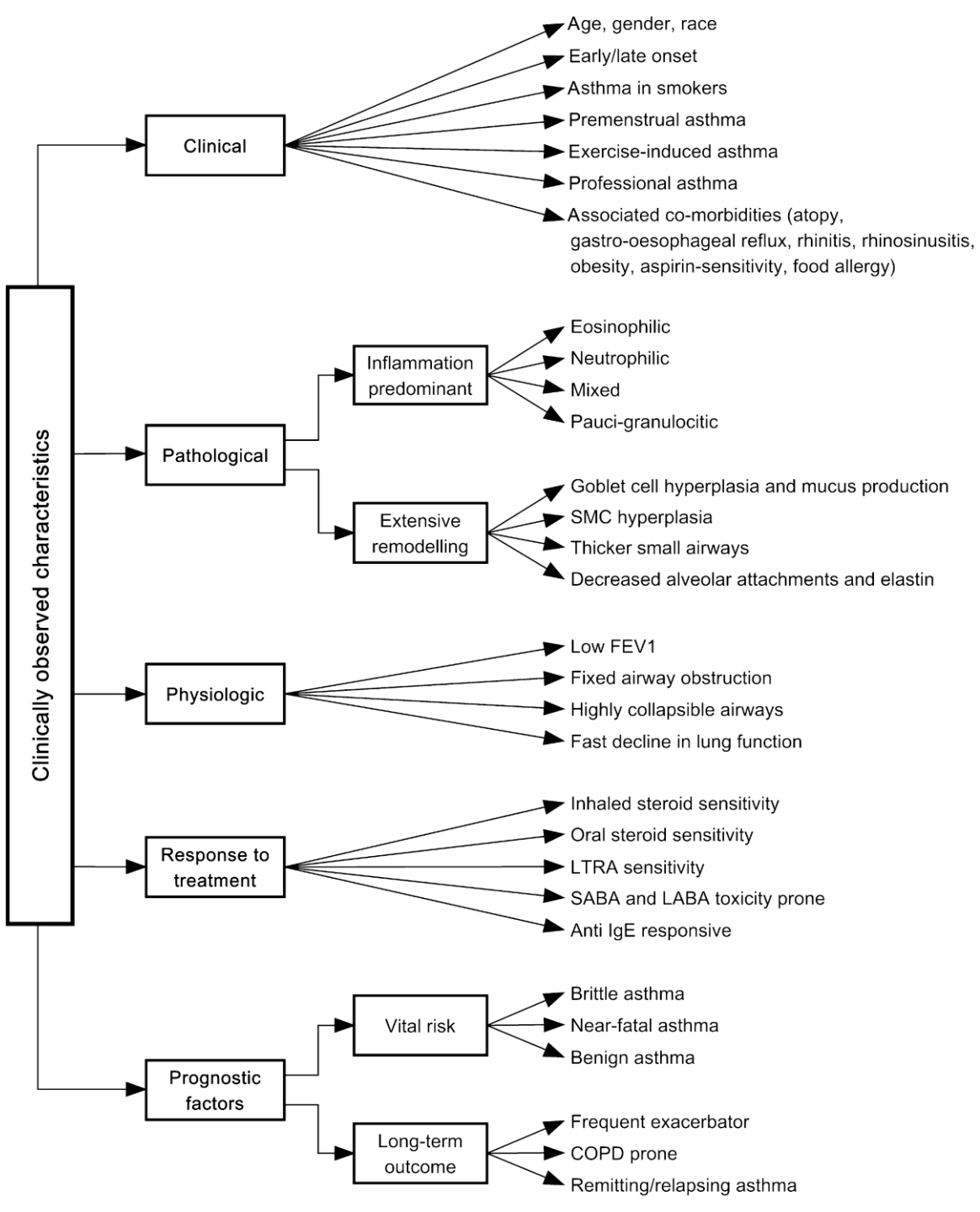
The hierarchy of asthma phenotypes/ endotypes



J Allergy Clin Immunol. 2011;127:355-360


'Asthma'
Early onset
Symptoms
Exacerbations
FEV
Th2 inflammation
Th
Phenotype A
Phenotype B
Phenotype


Discordant symptoms
Monitoring inflammation allows down-titration of corticosteroids
Early symptom predominant
Early onset, atopic. Normal BMI. High symptom expression.
Concordan disease
Symptom-based approach to therapy titration may be sufficient.
Obese non-eosinophilic
Later onset, female preponderance. High symptom expression.
Early onset atopic asthma
Concordant symptoms, inflammation and airway dysfunction.
Monitoring inflamma targeted corticosteroid exacerbation frequenc
Benign asthma
Mixed middle-aged cohort Well controlled symptoms and inflammation. Benign prognosis.
Inflammation predomina
Late onset, greater proportion
Few daily symptoms but a eosinophilic inflammatio
Symptoms
Eosinophilic inflammation


Clinically observed characteristics
Clinical
Age, gender, race
Early/late onset
Asthma in smokers
Premenstrual asthma
Exercise-induced asthma
Professional asthma
Associated co-morbidities (atopy, gastro-oesophageal reflux, rhinitis, rhinosinusitis, obesity, aspirin-sensitivity, food allergy)
Pathological
Inflammation predominant
Eosinophilic
Neutrophilic
Mixed
Pauci-granulocitic
Extensive remodelling
Goblet cell hyperplasia and mucus production
SMC hyperplasia
Thicker small airways
Decreased alveolar attachments and elastin
Physiologic
Low FEV1
Fixed airway obstruction
Highly collapsible airways
Fast decline in lung function
Response to treatment
Inhaled steroid sensitivity
Oral steroid sensitivity
LTRA sensitivity
SABA and LABA toxicity prone
Anti IgE responsive
Prognostic factors
Vital risk
Brittle asthma
Near-fatal asthma
Benign asthma
Long-term outcome
Frequent exacerbator
COPD prone
Remitting/relapsing asthma

Rationales of Phenotyping/endotyping

- The clinical, physiological and inflammatory presentation of the asthma syndrome is complex & heterogeneous
  - Necessity for
    - Prediction of clinical outcomes
    - Determining specific treatments

- Advances in our understanding and interpretation of this complexity through the analysis of inflammatory markers in well-defined patient cohorts

- The characterization of a Th2-high molecular phenotype has enabled the development of specific targets towards components of the Th2 inflammatory cascade

- Phenotyping will ensure that targeted therapeutic agents will be tailored and delivered to the ‘right’ patient at the ‘right’ time

Approaches for Phenotyping

- Phenotypes classified into broad categories based upon a single variable
  - including symptomatic triggers, patterns of airflow obstruction, and disease severity (eg. atopic status)
- Cluster analyses
  - Three large analyses in Europe (Haldar *et al.*, 2008; Siroux *et al.*, 2011) and the United States (Moore *et al.*, 2010)
    - based upon age of onset of asthma, gender, allergic status, asthma symptoms, and lung function as well as other factors that varied between the 3 studies
- Phenotyping based on inflammatory biomarkers
  - Inflammatory cells
  - FeNO

Haldar P et al., *Am J Respir Crit Care Med* 178(3):218-224, 2008.
Siroux V, et al., *Eur Respir J* 38(2):310-317, 2011.
Moore WC et al., *Am J Respir Crit Care Med* 181(4):315-323, 2010.

ORIGINAL ARTICLE

Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations

Loren C. Denlinger[1], Brenda R. Phillips[2], Sima Ramratnam[1], Kristie Ross[3], Nirav R. Bhakta[4], Juan Carlos Cardet[5], Mario Castro[6], Stephen P. Peters[7], Wanda Phipatanakul[5], Shean Aujla[8], Leonard B. Bacharier[6], Eugene R. Bleecker[7], Suzy A. A. Comhair[9], Andrea Coverstone[6], Mark DeBoer[10], Serpil C. Erzurum[9], Sean B. Fain[1], Merritt Fajt[8], Anne M. Fitzpatrick[11], Jonathan Gaffin[5], Benjamin Gaston[3], Annette T. Hastie[7], Gregory A. Hawkins[7], Fernando Holguin[8], Anne-Marie Irani[12], Elliot Israel[5], Bruce D. Levy[5], Ngoc Ly[4], Deborah A. Meyers[7], Wendy C. Moore[7], Ross Myers[3], Maria Theresa D. Opina[7], Michael C. Peters[4], Mark L. Schiebler[1], Ronald L. Sorkness[1], W. Gerald Teague[10], Sally E. Wenzel[8], Prescott G. Woodruff[4], David T. Mauger[2], John V. Fahy[4], and Nizar N. Jarjour[1];

Abstract

Rationale: Reducing asthma exacerbation frequency is an important criterion for approval of asthma therapies, but the clinical features of exacerbation-prone asthma (EPA) remain incompletely defined.

Objectives: To describe the clinical, physiologic, inflammatory, and comorbidity factors associated with EPA.

Methods: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3 were analyzed. An exacerbation was defined as a burst of systemic corticosteroids lasting 3 days or more. Patients were classified by their number of exacerbations in the past year:

socioeconomic status) did not associate with exacerbation frequency in SARP-3; bronchodilator responsiveness also discriminated exacerbation proneness from asthma severity. In the SARP-3 multivariable model, blood eosinophils, body mass index, and bronchodilator responsiveness were positively associated with exacerbation frequency (rate ratios [95% confidence interval], 1.6 [1.2–2.1] for every log unit of eosinophils, 1.3 [1.1–1.4] for every 10 body mass index units, and 1.2 [1.1–1.4] for every 10% increase in bronchodilatory responsiveness). Chronic sinusitis and gastroesophageal reflux were also associated with exacerbation frequency (1.7 [1.4–2.1] and 1.6 [1.3–2.0]), even after adjustment for multiple factors. These effects were replicated in the SARP-1 + 2 multivariable model

EDITORIALS

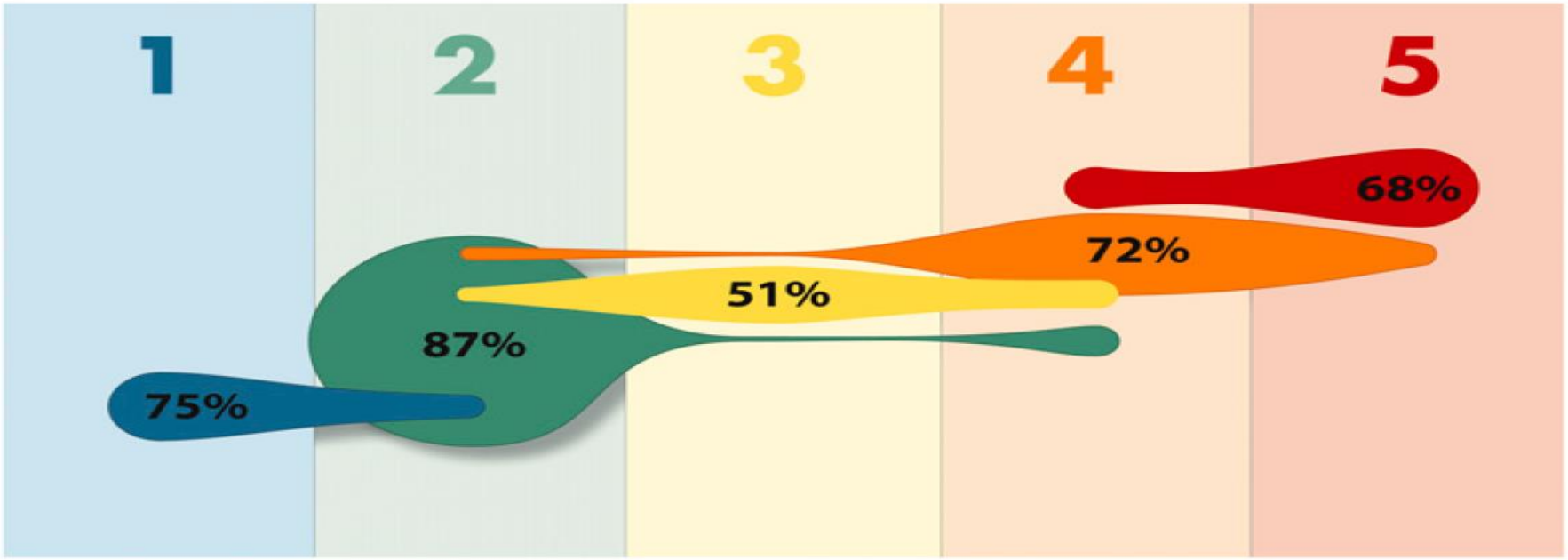
Exacerbation-Prone Asthma: A Separate Bioclinical Phenotype?

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],

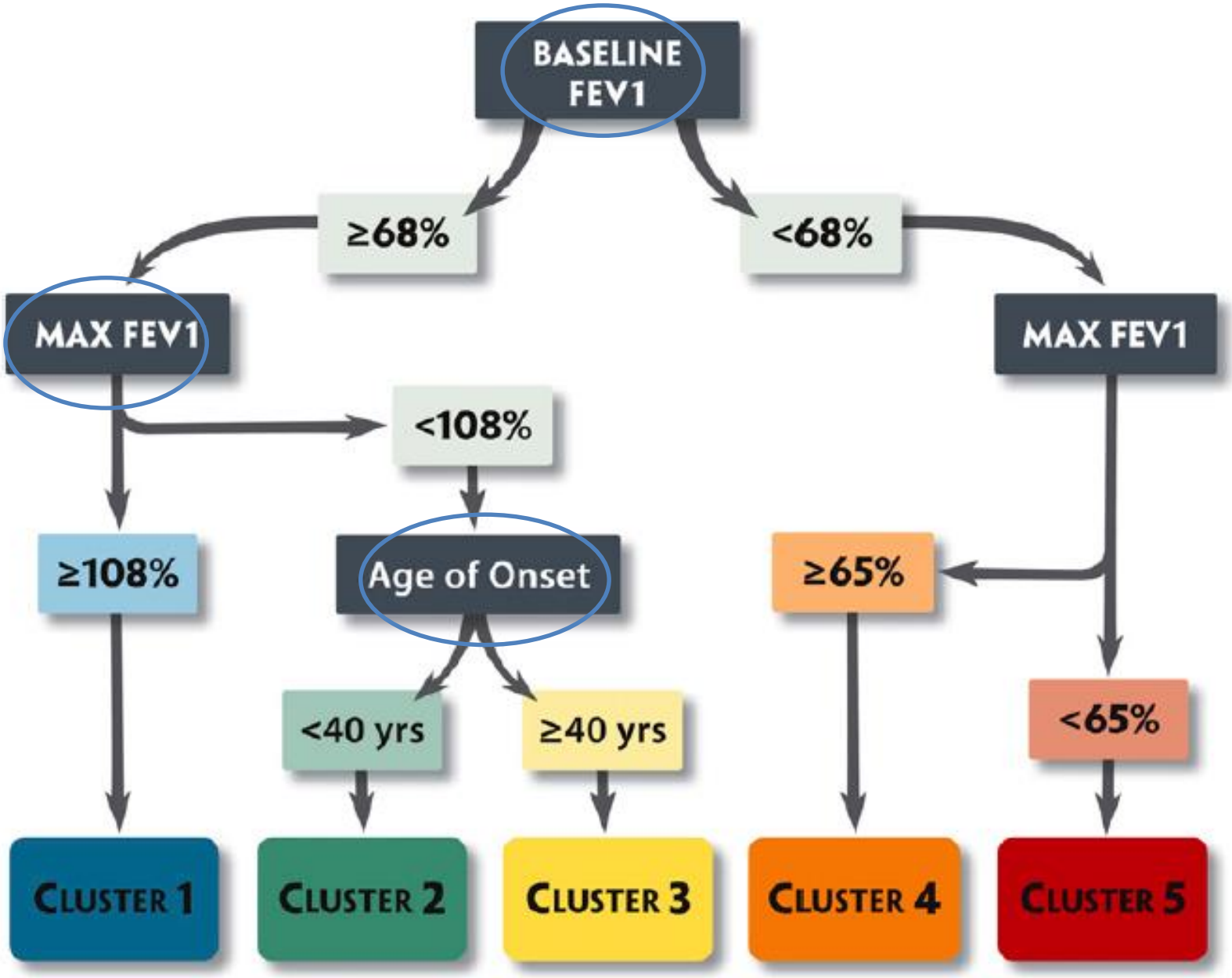
The Severe Asthma Research Program (SARP) cohort
Cluster analysis n=726
nonsmoking subjects with asthma (less than 5 pack-years of tobacco use) who met the ATS definition of severe asthma

and [2]Wake Forest University School of Medicine, Public Health Sciences, Winston-Salem, North Carolina



1	2	3	4	5
mild atopic asthma	mild to moderate atopic asthma	late onset non-atopic asthma	severe atopic asthma	severe asthma with fixed airflow

Am J Respir Crit Care Med Vol 181. pp 315–323, 2010



Am J Respir Crit Care Med Vol 181. pp 315–323, 2010

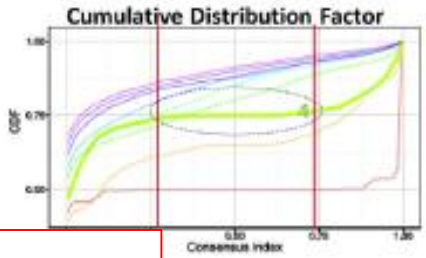
Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes

UBIOPRED Training Cohort
- 163 non-smoking severe asthma
- 53 smoker/ex-smoker severe asthma
- 50 mild-moderate asthma

Parameters

Age of asthma onset	FEV_1/FVC ratio
Pack-years of smoking	Asthma Control Questionnaire-5
Body Mass Index	Exacerbations in past year
FEV_1 % predicted	Oral Corticosteroid daily dose

Partition-around-medoids clustering
- Flat middle-part of Cumulative Distribution Factor
- Well-defined squares within Consensus Matrix
- Deviation from Ideal Stability Test



Sputum eosinophilia
FeNO
Serum Ig E

Phenotype T1
- Moderate-severe
- Well-controlled
- Medium-to-high inhaled corticosteroids
- Mild-none airflow obstruction

Phenotype T2
- Severe
- Late onset
- Smoker or Ex-smoker
- Severe airflow obstruction
- High blood eosinophil count

Phenotype T3
- Severe
- Oral corticosteroid-dependent
- Moderate-severe airflow obstruction

Phenotype T4
- Severe
- Female
- Mild-none airflow obstruction
- Frequent exacerbations

U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics

Diane Lefaudeux, MSc,[a]* Bertrand De Meulder, PhD,[a]* Matthew J. Loza, PhD,[b] Nancy Peffer, BS,[b] Anthony Rowe, PhD,[c] Frédéric Baribaud, PhD,[b] Aruna T. Bansal, PhD,[d] Rene Lutter, PhD,[e] Ana R. Sousa, PhD,[f] Julie Corfield, MSc,[g] Ioannis Pandis, PhD,[h] Per S. Bakke, MD,[i] Massimo Caruso, MD,[j] Pascal Chanez, MD,[k] Sven-Erik Dahlén, MD,[l] Louise J. Fleming, MD,[m] Stephen J. Fowler, MD,[n] Ildiko Horvath, MD,[o] Norbert Krug, MD,[p] Paolo Montuschi, MD,[q] Marek Sanak, MD,[r] Thomas Sandstrom, MD,[s] Dominic E. Shaw, MD,[t] Florian Singer, MD,[u] Peter J. Sterk, MD, PhD,[v] Graham Roberts, MD,[w] Ian M. Adcock, PhD,[m] Ratko Djukanovic, MD,[w] Charles Auffray, PhD,[a] Kian Fan Chung, MD,[m] and the U-BIOPRED Study Group‡

Lyon and Marseille, France; Spring House, Pa; High Wycombe, Cambridge, Stockley Park, Nottingham, London, Manchester, and Southampton, United Kingdom; Amsterdam, The Netherlands; Bergen, Norway; Catania and Rome, Italy; Molndal, Stockholm, and Umeå, Sweden; Budapest, Hungary; Hannover, Germany; Krakow, Poland; and Bern, Switzerland

J Allergy Clin Immunol. 2016 Oct 20. pii: S0091-6749(16)31185-X.

A Transcriptome-driven Analysis of Epithelial Brushings and Bronchial Biopsies to Define Asthma Phenotypes in U-BIOPRED

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Pascal Chanez[9]
Stephen Fowle
Yike Guo[1,2], Iar

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London, London,
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Ioannis Pandis[1,2],
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r, Germany; [12]Department
Biology and Medicine,
of Manchester,
gdom; and [17]Faculty of

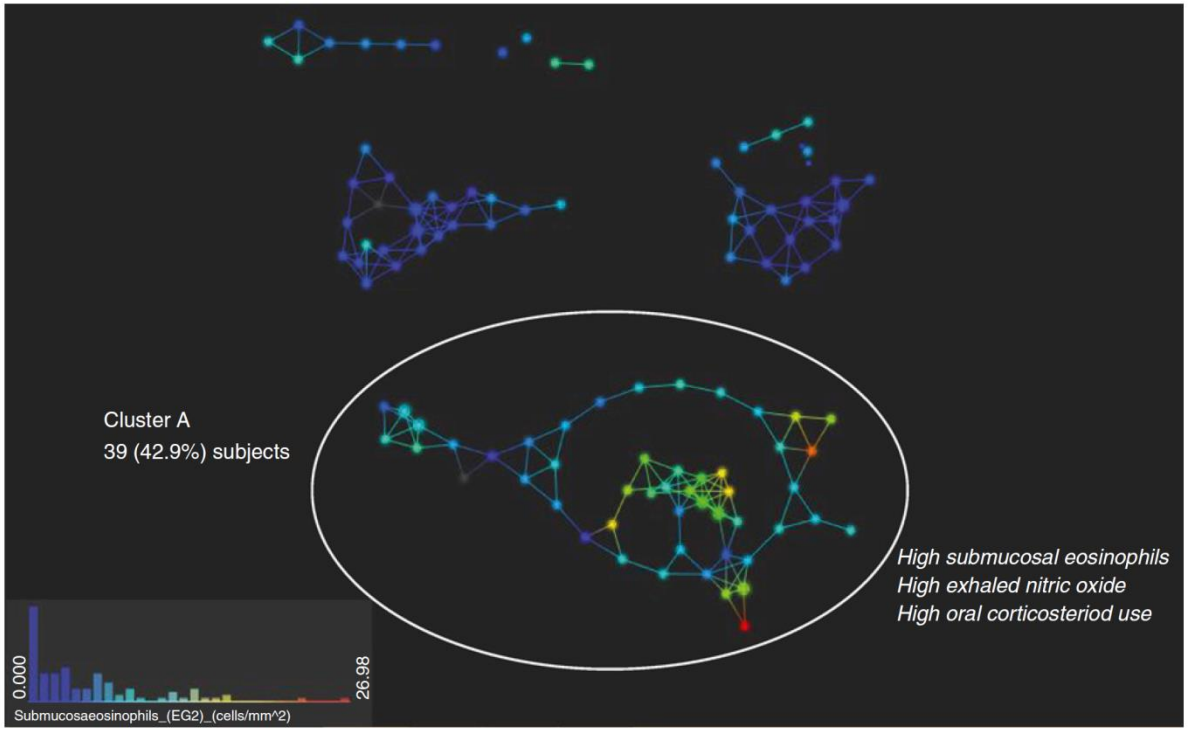


Figure 2. Topological network analysis of gene set variation analysis using 42 gene sets of relevance to the pathogenesis of asthma in bronchial biopsies revealing one large signature-driven cluster (cluster A) and four smaller distinct clusters. Cluster A was distinguished by higher submucosal eosinophil counts, higher levels of nitric oxide in exhaled breath, and higher oral corticosteroid use. The network is colored on the basis of the submucosal eosinophil count, with low cell count shown in *blue* and high cell count in *red*. The color key histogram (*bottom left*) shows the number of subjects with respect to the given cell count (*x-axis*) from low to high. Subjects with high submucosal eosinophil counts were noted to be highly enriched in cluster A as compared with the rest.

Am J Respir Crit Care Med Vol 195, Iss 4, pp 443–455, Feb 15, 2017

Considerations in application of phenotype/endotype during clinical practice

Asthma syndrome

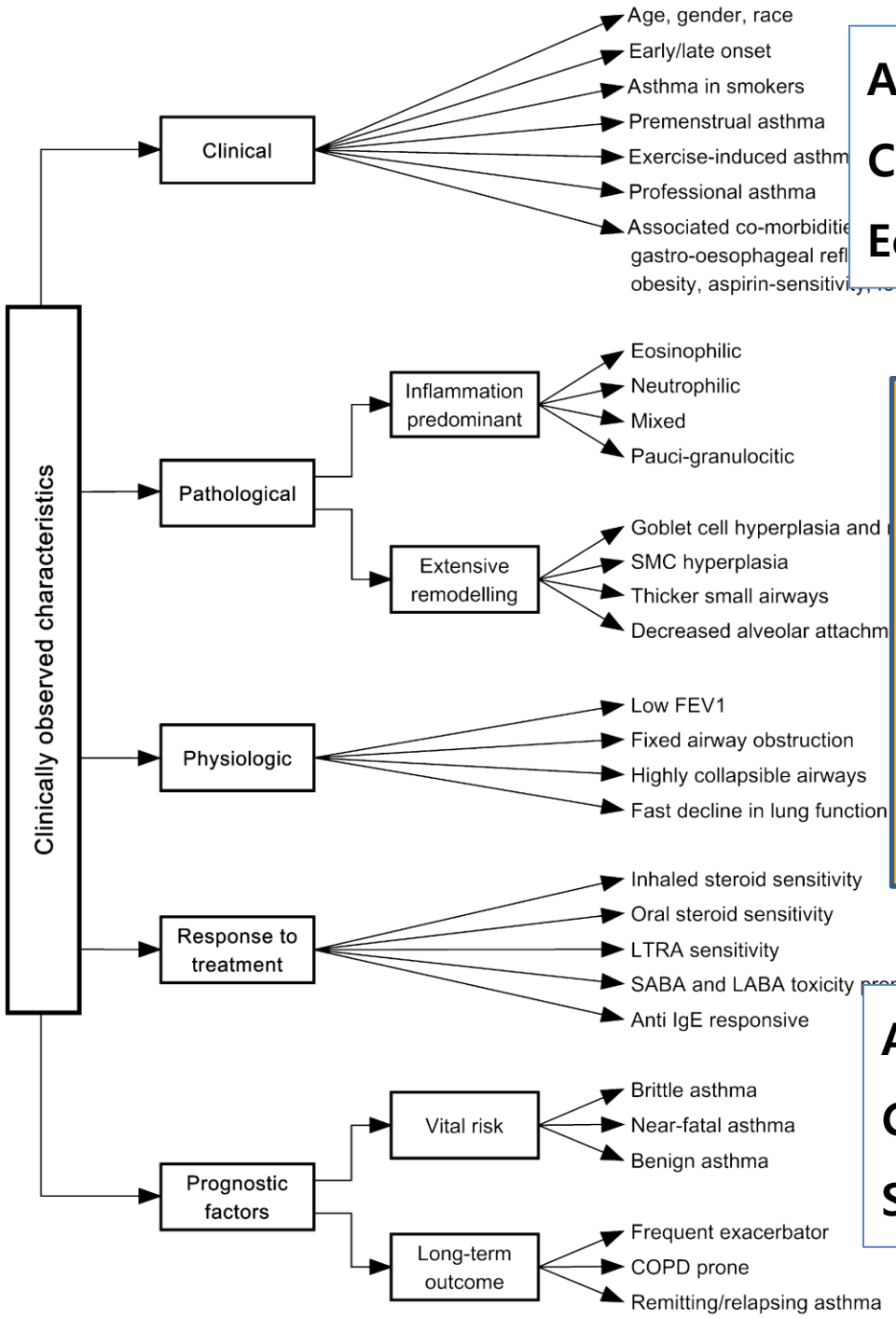
Phenotypes
Endotypes

Biomarkers

Impact on Treatment strategy

Outcomes & Prognosis
- Symptom control
- Future risk

Asthma phenotype/ Endotypes



Age or age of onset

Comorbidities

Eosinophilic vs Neturophilic

Implication on selecting therapeutic options

Applicability in clinical practice

Presence of applicable biomarkers etc.

Airflow limitation

Comorbidities

Steroid responsiveness

Currently available therapeutic options in management of BA

- Asthma medications (controller, reliever, add-on therapies)
  - ICS
  - LTRA
  - ICS/LABA
  - Theophylline
  - Tiotropium
  - Omalizumab, Mepolizumab
- Treating other modifiable risk factors
- Non-pharmacologic interventions
  - Cessation of smoking
  - Physical activity
  - Avoidance of occupational exposure
  - Avoidance of medications that may make asthma worse
  - Allergen immunotherapy, vaccination, bronchial thermoplasty

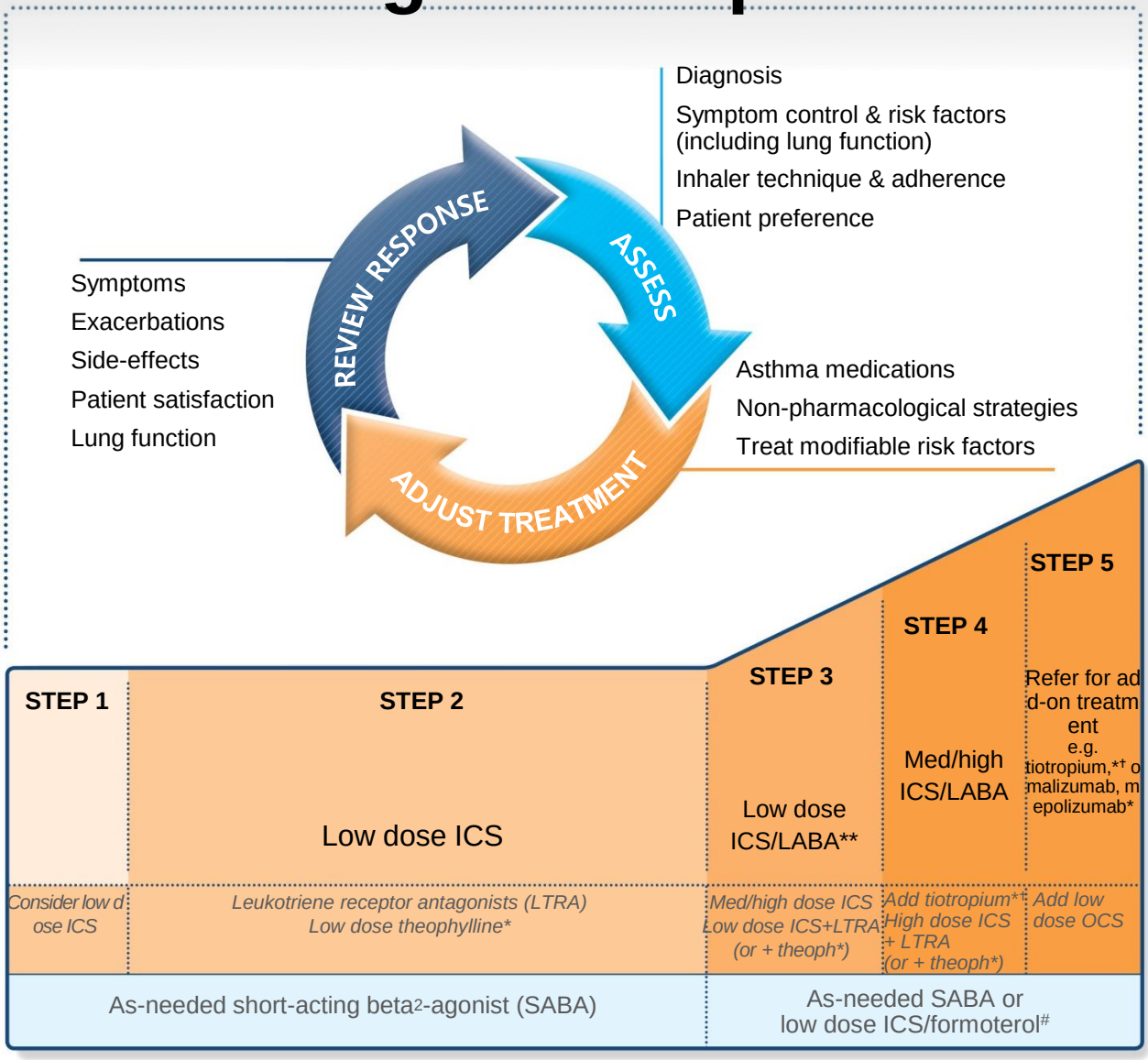
GINA 2016

Treatment Goals of Asthma

- Control of asthma and the prevention of risk of exacerbations and fixed airflow limitation.
  - Asthma control status
    - Questinnaires
    - Spirometry etc.
  - Biomarkers
    - Inflammatory

Stepwise management - pharmacotherapy

UPDATED!



*Not for children <12 years

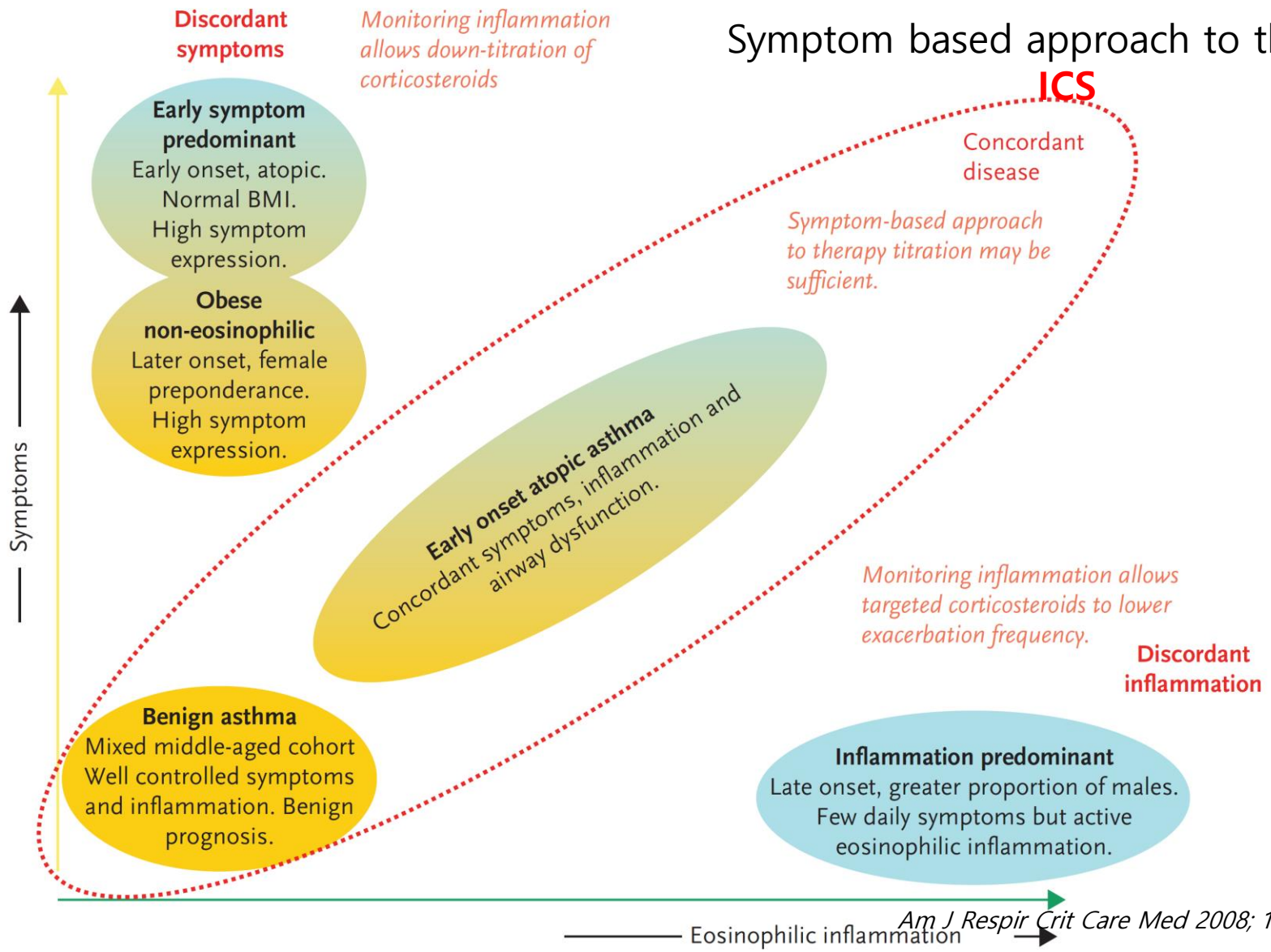
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

GINA 2016, Box 3-5 (1/8)

Symptom based approach to therapy titration



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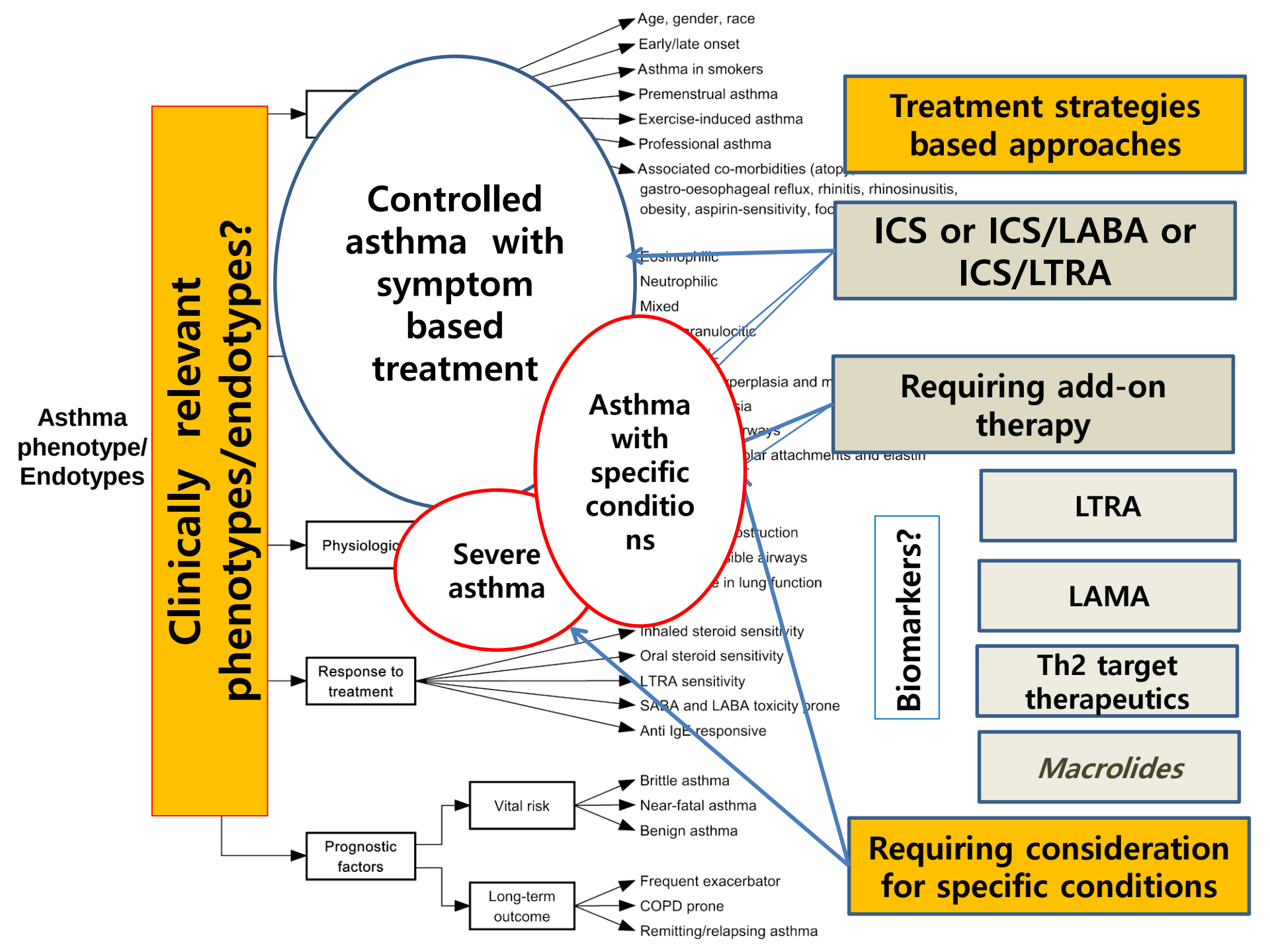
Asthma phenotype/ Endotypes
Clinically relevant phenotypes/endotypes?
Controlled asthma with symptom based treatment
Asthma with specific conditio ns
Severe asthma
Age, gender, race
Early/late onset
Asthma in smokers
Premenstrual asthma
Exercise-induced asthma
Professional asthma
Associated co-morbidities (atop
gastro-oesophageal reflux, rhinitis, rhinosinusitis,
obesity, aspirin-sensitivity, foo
Eosinophilic
Neutrophilic
Mixed
ranulocitic
perplasia and m
sia
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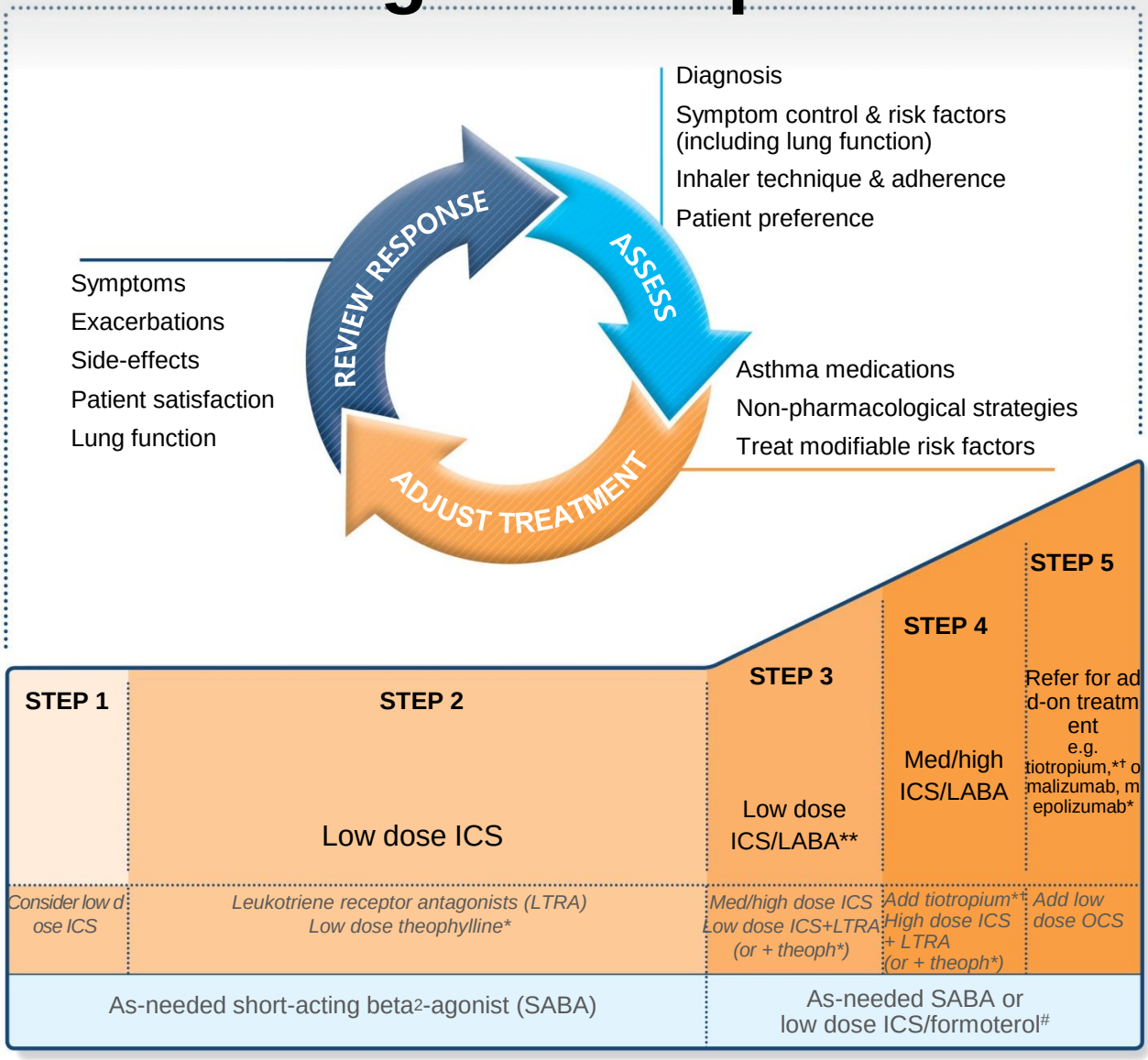
Anti IgE responsive
Prognostic factors
Vital risk
Brittle asthma
Near-fatal asthma
Benign asthma
Long-term outcome
Frequent exacerbator
COPD prone
Remitting/relapsing asthma
Treatment strategies based approaches
ICS or ICS/LABA or ICS/LTRA
Requiring add-on therapy
LTRA
LAMA
Th2 target therapeutics
Macrolides
Biomarkers?
Requiring consideration for specific conditions

Stepwise management - pharmacotherapy

UPDATED!



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GINA 2016, Box 3-5 (1/8)

Severe Asthma

- "asthma that requires treatment with high dose inhaled CSs plus a second controller and/or systemic CSs to prevent it from becoming ''uncontrolled" or that remains ''uncontrolled" despite this therapy." (ATS/ERS 2014)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming ''uncontrolled'' or which remains ''uncontrolled'' despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or ''not well controlled'' by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

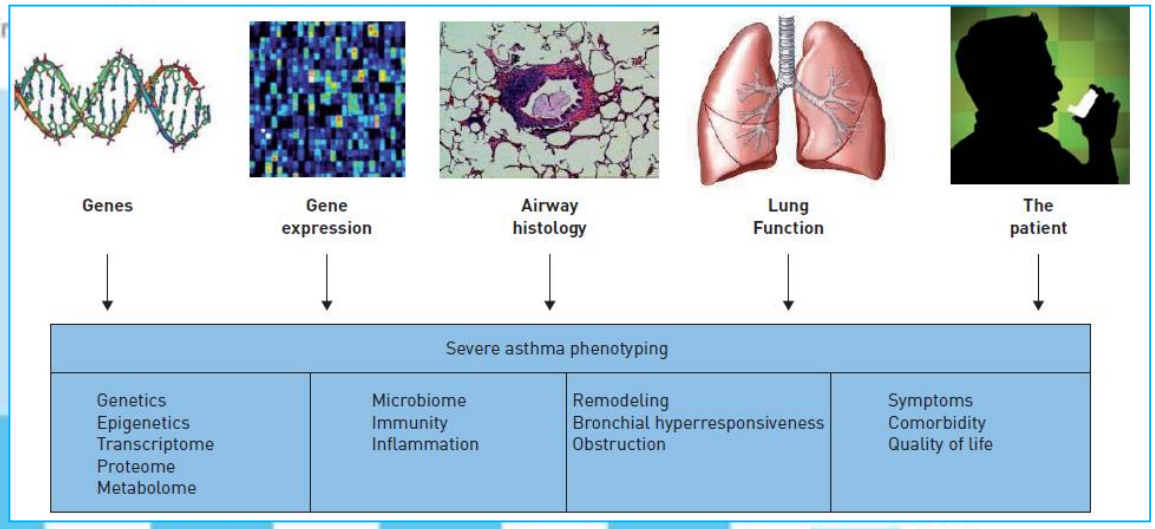
Eur Respir J 2014; 43: 343–373

Severe Asthma

Figure 2:

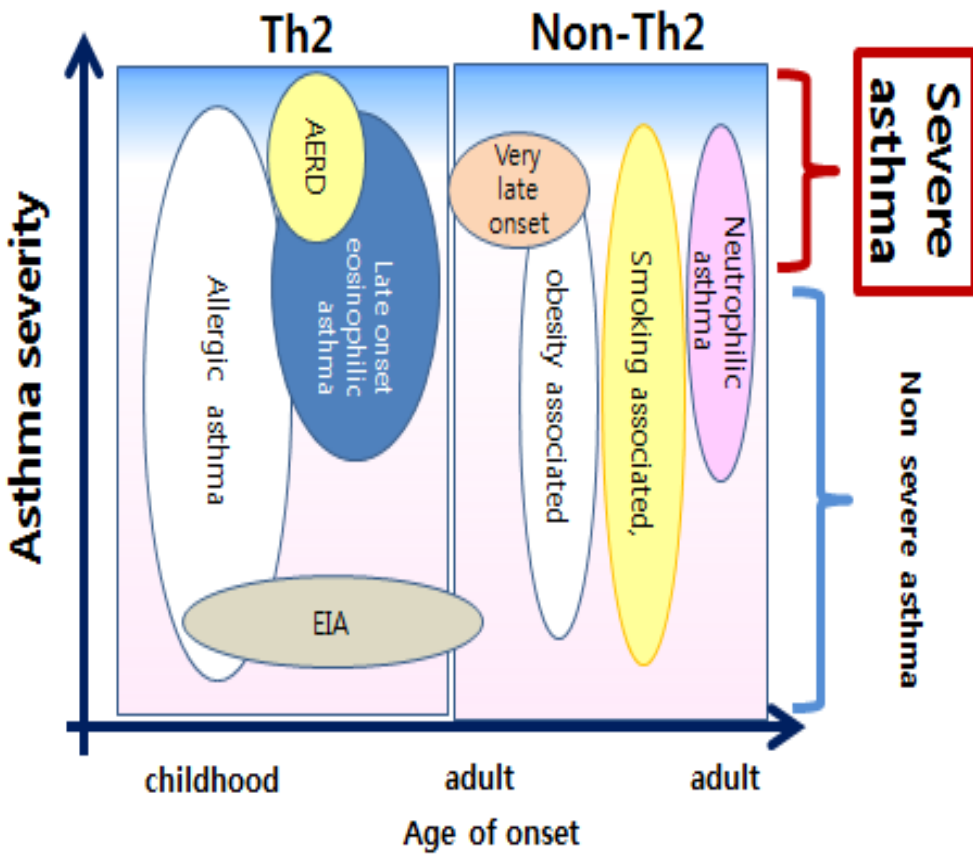
Proportions of participants with any asthma whose asthma was graded Severe, Moderate or Mild in the AIRE studies

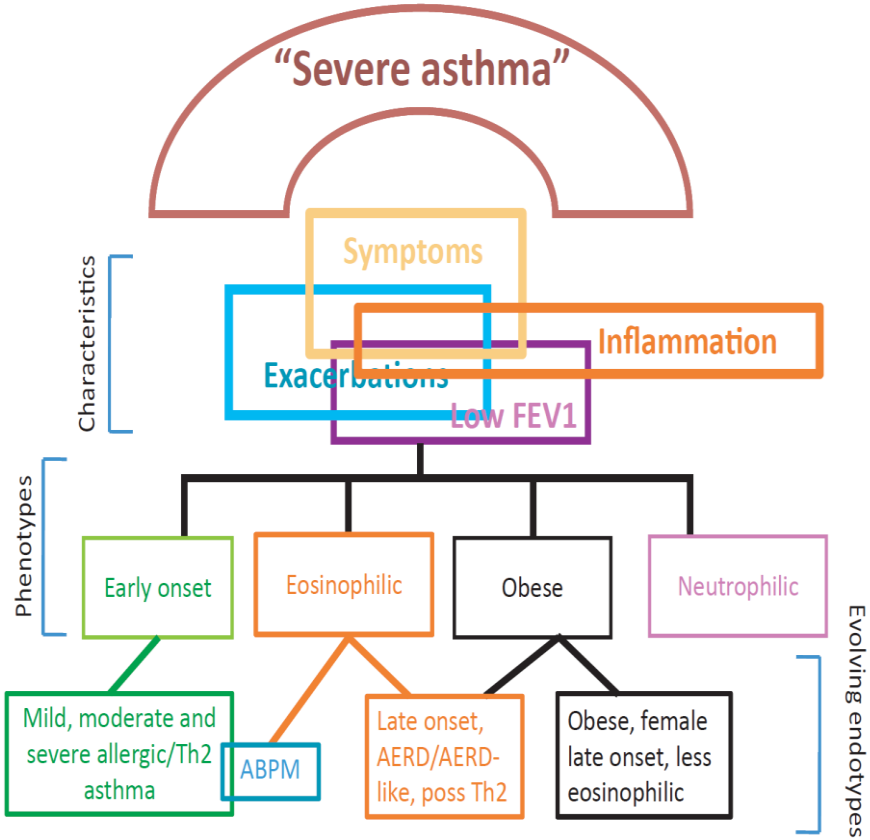
Source: Redrawn from data in Rabe K, et al., J Allergy Cli



http://www.globalasthmareport.org/

Heterogeneity of Severe Asthma

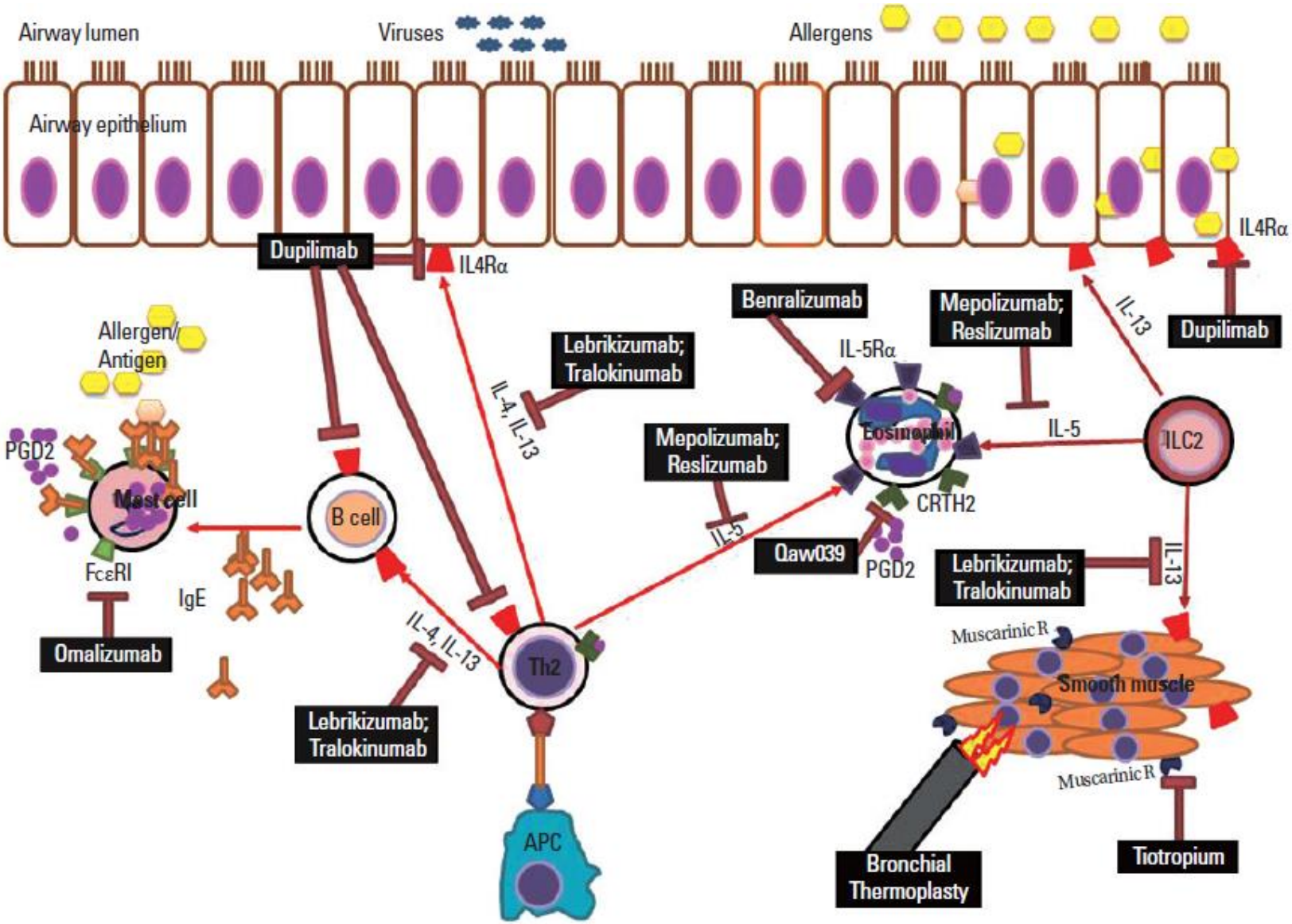




Korean J Med 2012;83:417-423

Clinical & Experimental Allergy, 42, 650–658

New target therapy for Severe Asthma



Allergy Asthma Immunol Res. 2017 January;9(1):3-14.

Approved therapies for severe asthma

General target	Specific target	Therapies used	Baseline medications	Major outcome
Smooth muscle tone	nerve	Tiotropium (inhaled)	ICS +LABA	↑ lung function, ↑time to severe asthma exacerbation, small ↓ exacerbation risk
Smooth muscle mass	none	Bronchial thermoplasty	ICS +LABA	↓ severe exacerbations, modest ↑ asthma QOL and ↓ Health care utilization at 12 months
Mast cells/ Basophils	IgE (prevent binding to high affinity IgE receptor)	Monoclonal anti-IgE antibody: (SQ omalizumab)	ICS (no additional controllers) ICS+LABA (17% on OCS) *subanalyzed by **Type-2 High Phenotype** (↑ FeNO, blood eosinophils or serum periostin)	↓ asthma exacerbations, ↓ serum free IgE, ↓ ICS dose ↓ asthma exacerbations and ↑ asthma QOL; *Greater effect
Eosinophils	IL-5	Anti-IL5 (IV or SQ mepolizumab) Anti-IL5 (SQ mepolizumab)	ICS + LABA; +/- OCS with **Type-2 High Phenotype** (sputum eosinophils >3% or ↑ blood eosinophils or ↑ FeNO) ICS + additional controller; 100% on systemic CS with **Type-2 High Eosinophilic phenotype** (blood eosinophils ≥300/μL prior year or ≥ 150/μL during optimization)	↓ asthma exacerbations, ↓ eosinophils in blood/sputum, ↑ AQLQ, ↑ symptom scores, ↑ lung function, ↓ systemic steroid requirements, ↓ exacerbations, ↑ AQLQ, ↑ asthma control

Allergy Asthma Immunol Res. 2017 January;9(1):3-14.

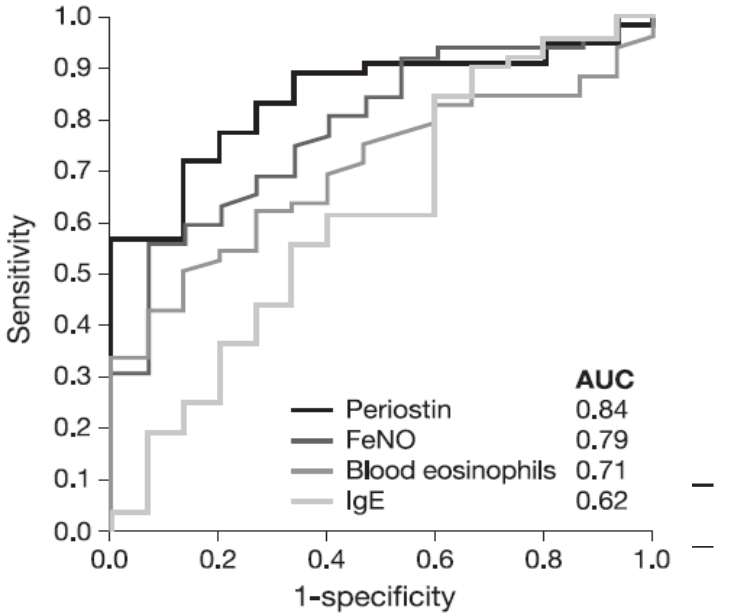
Therapies targeting neutrophils

General target	Specific target	Therapies used	Baseline medications	Major outcome
Th17 cells/ Neutrophils	IL-17R (blocks receptor binding to IL-17A, IL-17F, and IL-17E/ IL-25)	Anti-IL-17 receptor Ab (brodalumab SQ)	ICS+additional controller	No treatment differences vs placebo; Minimal improvements in ACQ seen only in a high-reversibility subgroup, no effect by blood neutrophils or eosinophil subgrouping
Neutrophils	CXCR2 (IL-8 receptor)	Selective CXCR2 receptor antagonist (SCH527123 oral)	ICS+additional controller, Sputum neutrophils >40%	↓ neutrophils (blood and sputum), slight ↓ mild exacerbations, no other clinical benefits observed
Bacteria or Neutrophils	50S subunit of bacterial ribosomes	Oral macrolide antibiotics (Azithromycin oral)	ICS+LABA with **low evidence for Type-2 inflammation** (low FeNO)	No difference in severe exacerbations and lower respiratory tract infections *Post-hoc sub-analysis of subgroup with the **lowest Type-2 inflammation** (no/low eosinophils and low FeNO): lower rate of exacerbations and infections vs placebo

Anti-Ig E/ Anti-IL5

- Anti-Ig E
  - High Th2 phenotype
    - ↑ FeNO, blood eosinophils or serum periostin
- Anti-IL5
  - High Th2 phenotype
    - sputum eosinophils >3% or ↑ blood eosinophils or ↑ FeNO
  - Eosinophilic
    - blood eosinophils ≥300/μL prior year or ≥ 150/μL during optimization

Biomarkers in type 2 cytokine-mediated asthma



J Allergy Clin Immunol 2012; 130:647–54

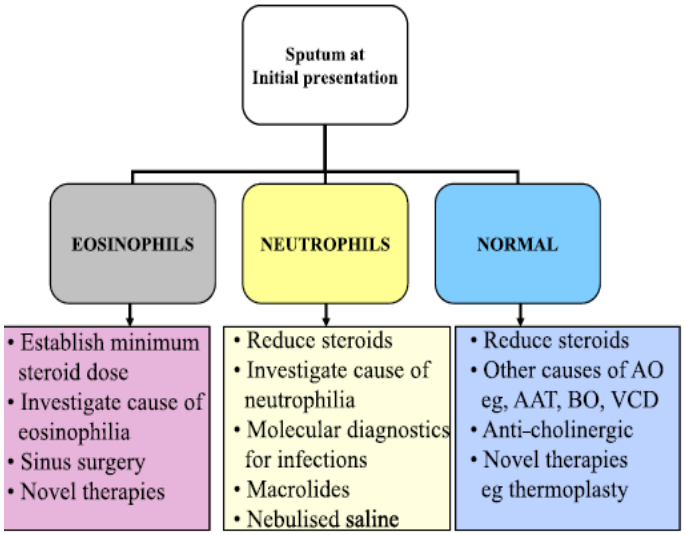
	Ideal characteristics of biomarker					
Biomarker	Easily measurable	Ability to distinguish a mechanism causally linked to important clinical outcome	Reliable and reproducible in the clinical setting	Ability to provide information about disease prognosis and clinical outcomes	Mechanistically linked to the therapeutic target	Cost-effective
Bronchial biopsy	–	++	–	–	++	–
Bronchoalveolar lavage	–	++	–	–	++	–
Sputum induction	+	++	–	+++	+	+
FeNO	++	++	+++	++	++	++
VOCs	++	+++	+	–	++	?
Exhaled breath condensate	+++	+	–	++	++	?
Exhaled breath temperature	+++	–	–	+	+	+++
Blood eosinophil counts	+++	+++	+++	++	+++	+++
Activation profile of eosinophils	+	++	–	–	+++	?
Serum periostin	+++	+++	+++	+++	+++	+++
Chitinase-like protein YKL-40	+	–	–	–	+	?
Blood ILC2s	–	+++	–	++	++	?
Serum IgE	+++	–	–	+	+	?

FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ILC2s, type 2 innate lymphoid

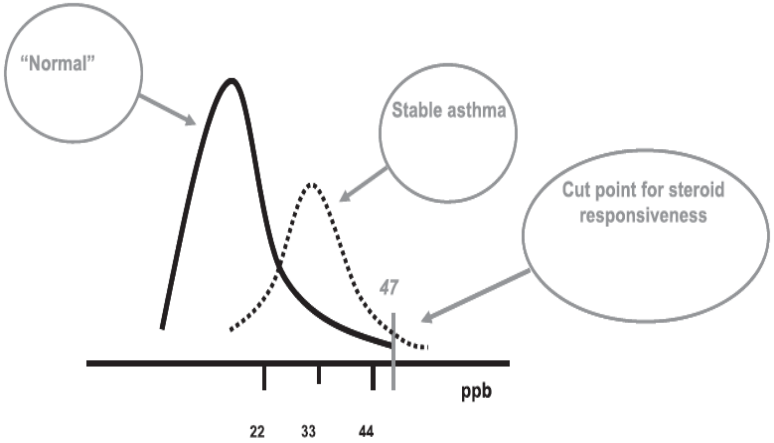
Clinical & Experimental Allergy, 47 : 148–160

Biomarkers Guided Treatment Strategies & relevant phenotypes

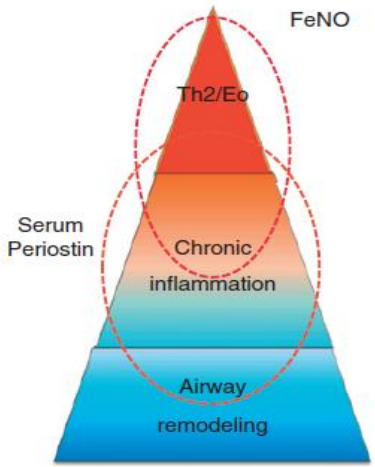
- Induced sputum



- FeNO



- Serum periostin



CHEST / 139 / 6 / JUNE, 2011

Am J Respir Crit Care Med Vol 184. pp 602–615, 2011

Allergology International. 2014;63:153-160

A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils)

H L Petsky,[1,4] C J Cates,[2] T J Lasserson,[2] A M Li,[3] C Turner,[4] J A Kynaston,[5] A R Chang[1,6]

Figure 3 Number of subject who had ≥1 exacerbation over the study period (sputum eosinophils (SpEos)).

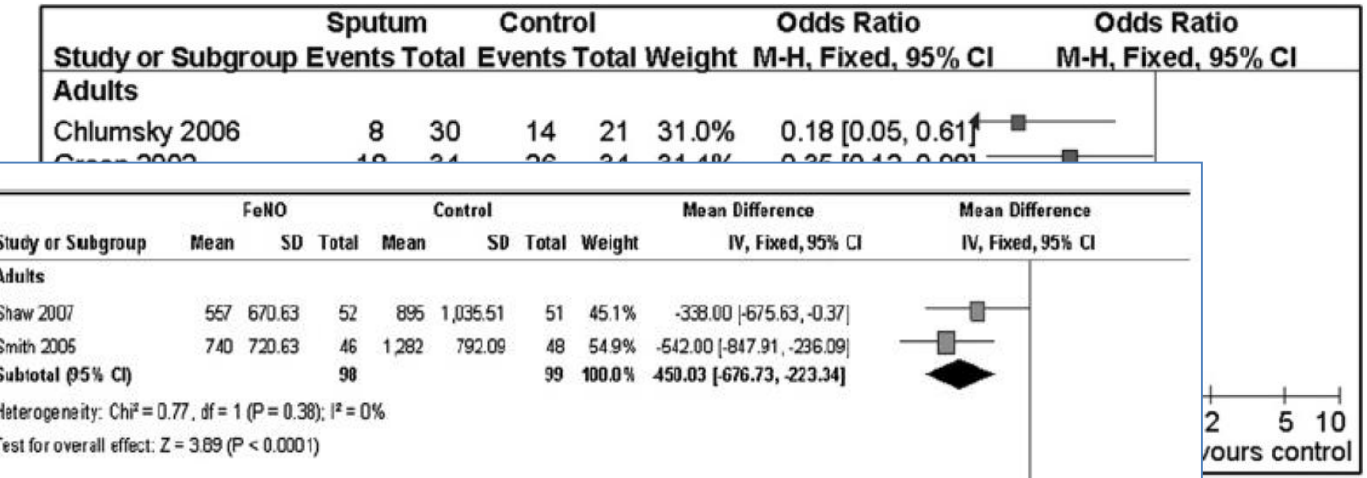


Figure 4 Inhaled corticosteroid dose at final visit (fractional exhaled nitric oxide (FeNO)).

Thorax 2012;67:199e208.

Exhaled nitric oxide levels to guide treatment for adults with asthma

Helen L Petsky[1], Kayleigh M Kew[2], Cathy Turner[3], Anne B Chang[1,4]

Tailoring asthma treatment using FeNO versus clinical symptoms

Patient or population: adults with asthma
Setting: outpatient
Intervention: asthma treatment tailored on FeNO
Comparison: asthma treatment tailored on clinical symptoms

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with asthma treatment tailored on clinical symptoms**	Risk with asthma treatment tailored on FeNO				
Number of participants who had ≥ 1 exacerbations over study period Follow-up: range 18 weeks to 52 weeks	**25 per 100**	**17 per 100** (13 to 22)	**OR 0.60** (0.43 to 0.84)	1005 (5 RCTs)	⊕⊕⊕◯ MODERATE[1]	-
Number of exacerbations per 52 weeks (exacerbation rates) Follow-up: mean 52 weeks	The control group ranged from 0.23 to 0.9 exacerbations per 52 weeks	**Rate ratio 0.59** (0.45 to 0.77)	-	842 (5 RCTs)	⊕⊕⊕◯ MODERATE[1]	-
ICS dose at final visit Follow-up: range 18 weeks to 52 weeks	The mean ICS dose taken by the control group at final visit was **659 mcg**	The mean ICS dose taken in the FeNO groups was 17.01 lower (101.75 lower to 67.72 more) **577 mcg**	-	582 (4 RCTs)	⊕⊕◯◯ VERY LOW[2,3]	A random-effects sensitivity analysis gave a very imprecise result: MD -147.15 (95% CI -380.85 to 86.56)

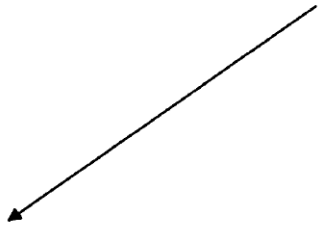
***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**The control group risks were calculated as a mean of the scores or events in the control groups of the studies contributing to each analysis. We could not calculate a control risk for the number of exacerbations per 52 weeks because we did not have information for each arm of the studies, just ratios between them.
CI: confidence interval; **FeNO:** fractional exhaled nitric oxide; **ICS:** inhaled corticosteroids; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial

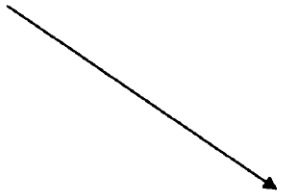
Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011440

Biomarkers Guided Treatment Strategies in Adult Patients with Asthma

A possible algorithm in patients where inflammatory assessment is applicable

Sputum eosinophils >3% & Blood eosniphils >150 measured twice or >300 measured once
FeNO>50ppb
High Periostin (if a specific cut off value is determined)





Titrate the dose of ICS based on the above
Consider anti-IgE if criteria exist
Consider anti-Il-5 if criteria exist
Consider anti-IL-13 if criteria exist

If none of the above exist
Consider increase of bronchodilators
Alternative treatment options (macrolides, Thermoplasty)

Arch. Immunol. Ther. Exp. (2017) 65:1–9

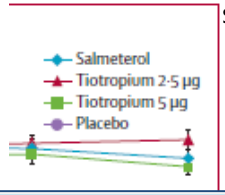
LAMA

- Add-on therapy on symptom based approaches
  - Tiotropium by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations (GINA 2016)
    - Symptomatic patients requiring bronchodilation
    - Frequent exacerbators
- Asthma with airflow limitation
  - ACOS
  - Asthma in elderly
- Others
  - *Neutrophilic asthma?*
  - *Smoker with asthma?*

Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011721
Kerstjens HA, Lancet Respir Med 2015; 3:367–376
Kerstjens HA , N Engl J Med 2012; 367:1198–1207

LAMA versus placebo in adults with asthma taking background LABA/ICS

Patient or population: adults with asthma
Setting: outpatient
Intervention: LAMA + background LABA/ICS
Comparison: LABA/ICS alone
The studies randomised participants to LAMA or placebo and required participants to be taking background LABA/ICS
The durations shown are the weighted means of the studies included in each analysis



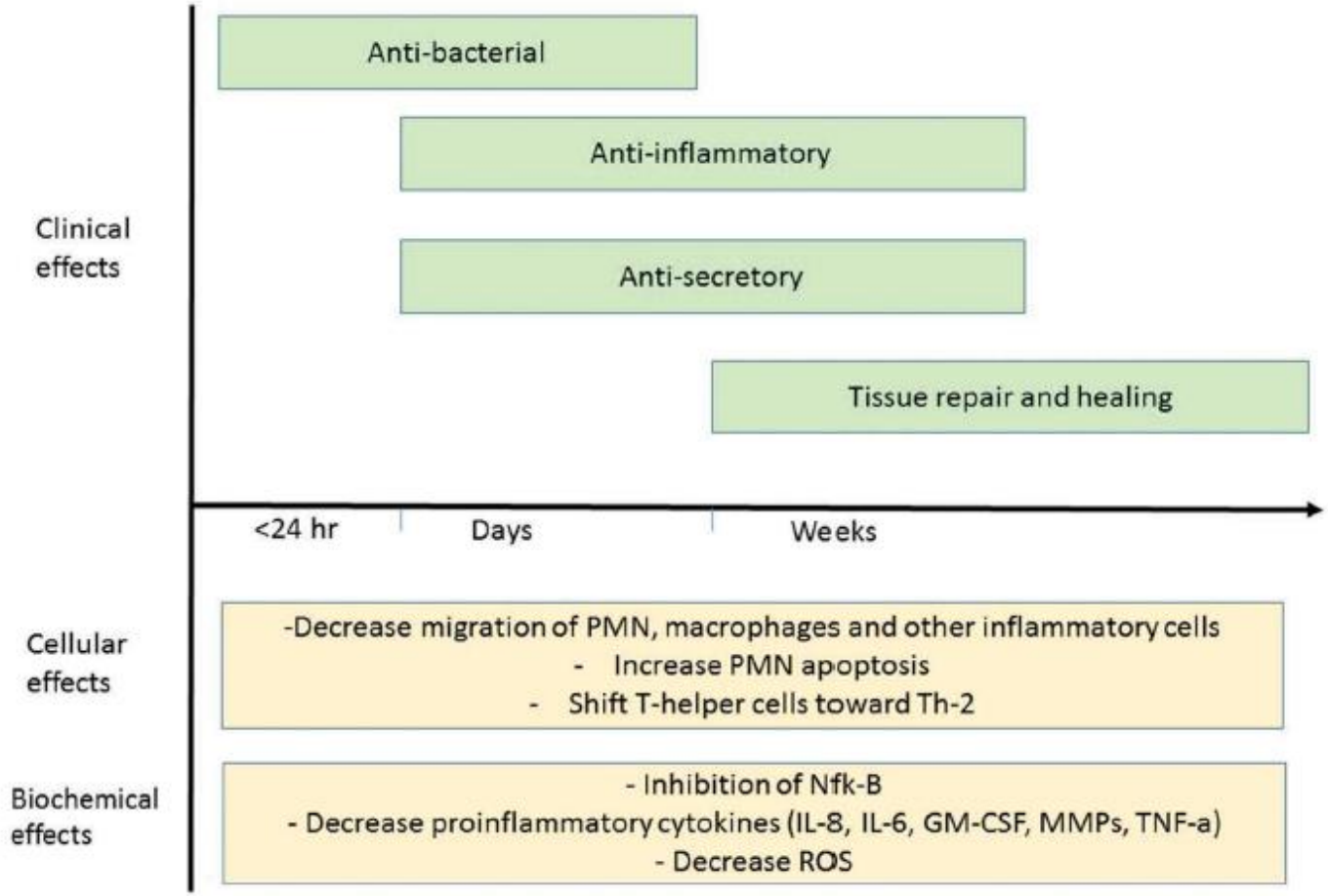
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with LABA/ICS	Risk with LAMA + LABA/ICS				
Exacerbations requiring oral corticosteroids 48 weeks	**328 per 1000**	**271 per 1000** (218 to 333)	**OR 0.76** (0.57 to 1.02)	907 (2 RCTs)	⊕⊕⊕◯ Moderate[1]	Analyses comparing the number of exacerbations per patient in each group (rate ratio) and the time until first exacerbation (hazard ratio) were in keeping with the main result
Exacerbations requiring hospital admission 49 weeks	**43 per 1000**	**30 per 1000** (15 to 59)	**OR 0.68** (0.34 to 1.38)	1191 (3 RCTs)	⊕⊕◯◯ Low[5,6]	Too few events to detect whether there is a benefit of LAMA add-on
Lung function (change in trough FEV_1 L) 49 weeks	The mean change in trough FEV_1 was **0.08 L**	The mean change in trough FEV_1 (L) in the intervention group was **0.07 higher** (0.03 higher to 0.11 higher)	-	1191 (3 RCTs)	⊕⊕⊕⊕ High[7]	Some benefit of LAMA add-on over LABA/ICS alone
Asthma control (ACQ) 7-point scale from 0 to 6 Lower scores are better 48 weeks	The mean asthma control (ACQ) was **2.13**	The mean asthma control (ACQ) in the intervention group was **0.13 better** (0.23 better to 0.02 better)	-	907 (2 RCTs)	⊕⊕⊕⊕ High	Scores with LAMA add-on were better than LABA/ICS alone, but the difference was not clinically significant (MCID = 0.5)
Any adverse events 49 weeks	**813 per 1000**	**753 per 1000** (693 to 803)	**OR 0.70** (0.52 to 0.94)	1197 (3 RCTs)	⊕⊕⊕⊕ High[7]	The listed events were reported in at least 2% of patients who underwent randomisation

LTRA

- Add-on therapy on symptom based approaches
  - Comorbid with allergic rhinitis
  - Younger, shorter duration of asthma

- AERD
- Exercise-induced bronchoconstriction (EIB)
- Smoker with asthma etc.

Macrolides



Postgraduate Medicine, (2017)DOI: 10.1080/00325481.2017.1285677

Macrolide versus placebo for chronic asthma

Patient or population: adults and children with chronic asthma
Settings: outpatient
Intervention: macrolide
Drugs used were clarithromycin, azithromycin, roxithromycin and troleandomycin. Macrolide was given once or twice daily in most studies for between 6 and 52 weeks (median 8 weeks).
Comparison: placebo
Durations were calculated as weighted means of the studies included in each analysis

Outcomes[a]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Macrolide			
'Severe' exacerbation - requiring at least OCS Number of people having one or more exacerbations requiring at least systemic steroids. Classification varied across studies 18 weeks	242 per 1000	208 per 1000 (121 to 334)	**OR 0.82** (0.43 to 1.57)	290 (5 RCTs)	⊕◯◯◯ very low[b,c,d]
Symptom scales 10 weeks	The symptom scales used were different across studies so it was not possible to calculate an assumed risk	The mean symptom scales in the intervention group was **0.35 standard deviations lower** (0.67 lower to 0.02 lower)	-	139 (4 RCTs)	⊕◯◯◯ very low[b,f,g,h]
Asthma control Scored from 0 to 6 (lower sco mer	The mean change in asthma control score in the control	The mean asthma control score in the intervention	-	353 (4 RCTs)	⊕◯◯◯ very low[b,c,i]

At this time, there is minimal evidence to support the use of azithromycin in patient with asthma. Similarly, azithromycin is not recommended in the management of patients with chronic rhinosinusitis with no confirmed or suspected infection

Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.:CD002997

Asthma phenotypes with specific conditions impacting on diagnosis and treatment of BA

- Allergic bronchopulmonary aspergillosis (ABPA)
- Exercise-induced bronchoconstriction (EIB)
- Aspirin-exacerbated respiratory disease (AERD)
- Asthma in workplace (AIW)
- Asthma in Elderly (AIE)
- Smoker with asthma

Allergic bronchopulmonary aspergillosis (ABPA)

Rosenberg-Patterson criteria[46,47]	Minimal essential criteria[51]	'Truly minimal' criteria[7]	ISHAM Working Group[29]	ABPA in CF[55]
Major criteria 1. Asthma 2. Presence of transient pulmonary infiltrates (fleeting shadows) 3. Immediate cutaneous reactivity to *Af* 4. Elevated total serum IgE 5. Precipitating antibodies against *Af* 6. Peripheral blood eosinophilia 7. Elevated serum IgE and IgG to *Af* 8. Central/proximal bronchiectasis with normal tapering of distal bronchi *Minor criteria* 1. Expectoration of golden brownish sputum plugs 2. Positive sputum culture for *Aspergillus* species 3. Late (Arthus-type) skin reactivity to *Af*	1. Asthma 2. Immediate cutaneous reactivity to *Af* 3. Total serum IgE >1,000 ng/mL (417 kU/L) 4. Elevated specific IgE-*Af*/IgG-*Af* 5. CB in the absence of distal bronchiectasis	1. Asthma 2. Immediate cutaneous reactivity to *Af* 3. Total serum IgE >1,000 ng/mL (417 kU/L) 4. CB in the absence of distal bronchiectasis	*Predisposing conditions* 1. Bronchial asthma 2. Cystic fibrosis *Obligatory criteria (both should be present)* 1. Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Af* 2. Elevated total IgE levels (>1,000 IU/mL)* *Other criteria (at least two of three)* 1. Presence of precipitating or IgG antibodies against *Af* in serum 2. Radiographic pulmonary opacities consistent with ABPA 3. Total eosinophil count >500 cells/μL in steroid naïve patients (may be historical) (*If the patient meets all other criteria, an IgE value <1,000 IU/mL may be acceptable)	Presence of two of the following three: (i) Immediate skin reactivity to *Af* antigens, (ii) Precipitating antibodies to *Af* antigens, (iii) Total serum IgE >1,000 IU/mL; and at least two of the following six: (i) Bronchoconstriction, (ii) Peripheral blood eosinophilia >1,000/μL, (iii) History of pulmonary infiltrates, (iv) Elevated specific IgE-*Af*/IgG-*Af*, (v) *Af* in sputum by smear or culture, (vi) Response to steroids

ABPA, allergic bronchopulmonary asperillosis; *Af*, *Aspergillus fumigatus*; CB, central bronchiectasis; CF, cystic fibrosis; IgE, immunoglobulin E; IgG, immunoglobulin G; ISHAM, International Society for Human and Animal Mycology.

Systemic corticosteroids

Antifungal agents

Omalizumab

Proc Am Thorac Soc Vol 7. pp 237–244, 2010

Allergy Asthma Immunol Res. 2016 July;8(4):282-297.

Aspirin-intolerant asthma (AIA); aspirin-exacerbated respiratory disease (AERD)

- 5–10% of all adult asthmatics and is more common in non-atopic asthmatics
- Female predominant - 5.5 : 1 to 1.32 : 1

- Starts with symptoms of rhinitis during the third decade, often after a viral respiratory illness. Over a period of months, chronic nasal congestion, anosmia, rhinorrhea, and nasal polyps develop, which are followed by asthma and sensitivity to aspirin

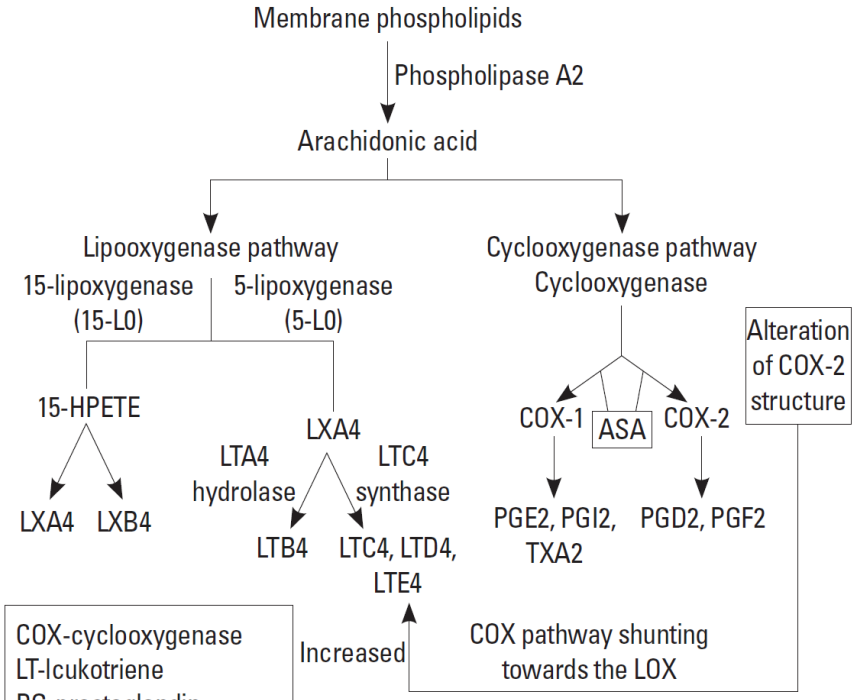
- Histologically, AERD is characterized by an intense eosinophilic inflammation of nasal and bronchial tissues

- Overproduction of cysteinyl leukotrienes (Cys-LTs), MCP-3 and RANTES

- Key diagnostic tools: lysine-aspirin bronchial challenge test or an oral challenge protocol

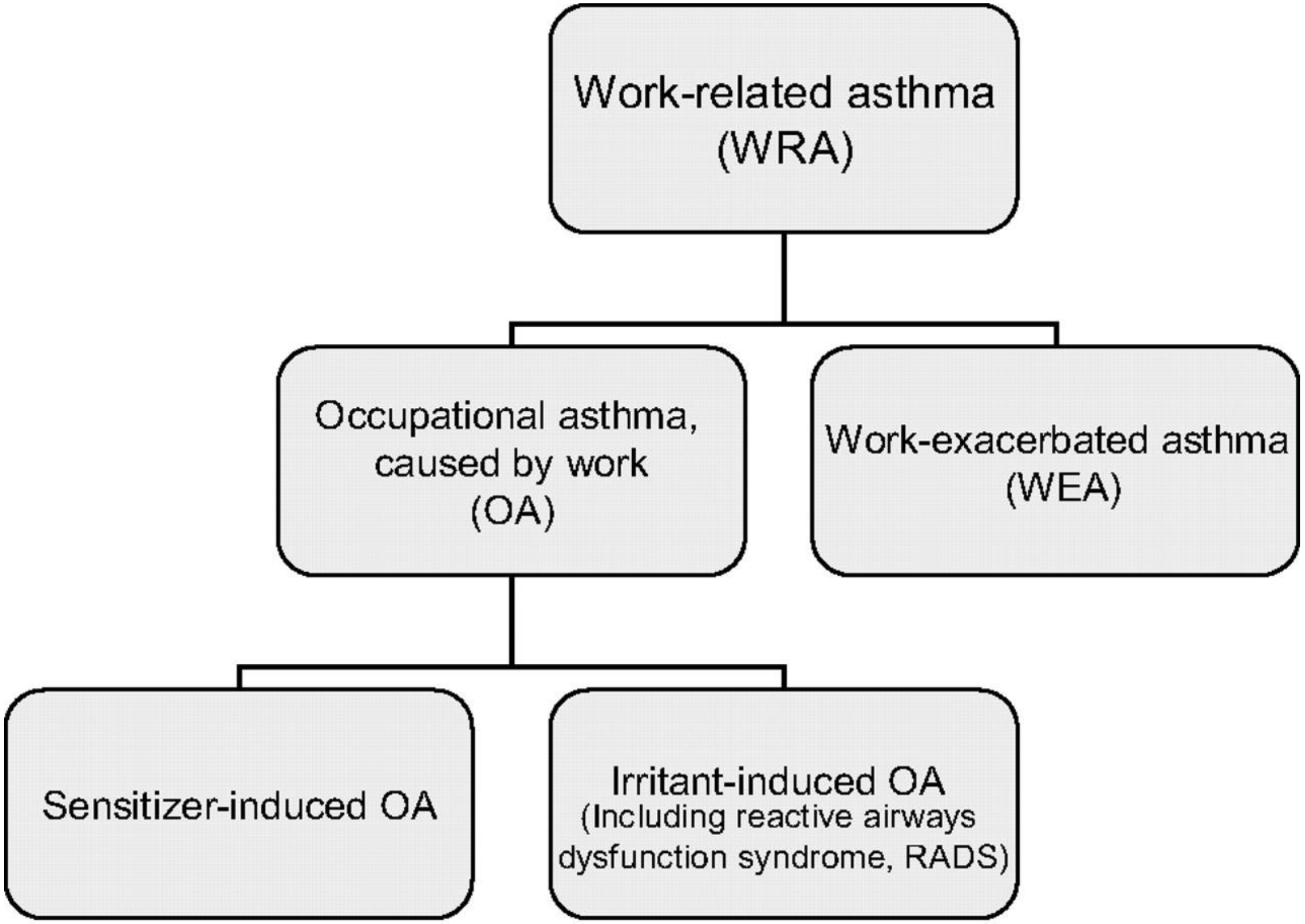
Genetic impact of SNPs in candidate genes of the arachidonic acid pathway on aspirin exacerbated respiratory disease

Gene	rs number	OR
LTC4S	rs730012	2.62 1.88 - -
CACNG6	rs192808 BL1_ht6	2.88 2.81
ALOX5	Sp1 binding motifs in tandem [G-C-G-A]	- 5.0
NAT2	-9246G>C [T-C-A-C-G-G]	1.61 1.62
CysLTR1	-634C>T -475A>C -336A>G 927T>C 899G/A	 2.89 - 9.78 6.28
CysLTR2	601G/A -1220A>C -819T>G +2078C>T +2534A>G	- - 2.04 2.28 2.02



Gene	rs number	OR
ADORA1	rs16851030 rs10920568 ht [A-C-G]	3.22 0.52 0.56
ADORA2A	ht [A-T]	0.33
GPR44	-466T>C	-
PTGER2	-12813G>A -10814T>A -6179A>G -616C>G -166G>A	3.21 - - 0.64 2.60
PTGER3	-1709T>A A>C A/G	3.02 1.31 1.36
PTGER4	-1254A>G	1.90
PTGIR	+1915T>C	0.37
TBXAS1	+141931T>A	0.27
TBXA2R	+795T>C +795T>C -4684C>T	- 2.57 0.42
RGS7BP	BL3_ht2	0.47

Fig. 2. Genetic impact of SNPs in candidate genes of the arachidonic acid pathway on aspirin exacerbated respiratory disease. Data are represented as odds ratios (OR). Taken with permission from Park, et al. Allergy Asthma Immunol Res 2013;5:258-76.[48] SNPs, single nucleotide polymorphisms.



These groupings are not mutually exclusive; e.g. OA can be followed by WEA

CHEST 2011; 139(3):674–681

Consider diagnosis in all patients with:
WRA symptoms, new asthma, and/or worsening asthma symptoms

Confirm Asthma and Onset
Medical history–childhood asthma, allergies
Symptoms – onset / nature / timing
Spirometry - bronchodilator response and/or airway reactivity–methacholine challenge
Medications

Asthma

Assess Exposures /Factors that Cause or Exacerbate Asthma
Occupational history
- Allergens, irritants
- Exertion, cold, infections
- Type of work process / setting
- Ventilation / use of respiratory protection
- Obtain MSDSs
- Co-workers – symptoms
- Magnitude / timing of exposures

Environmental history
- Pets, hobbies, home exposures, ambient air pollution

Atopy / allergies

No Asthma

Evaluate other causes of asthma-like symptoms*
- Vocal cord dysfunction
- Upper respiratory tract irritation
- Hypersensitivity pneumonitis
- Rhinosinusitis
- Psychogenic factors

**These conditions can co-exist with asthma*

Assess Relationship of Asthma to Work**
Symptoms – onset / timing /severity related to work, other environments
Physiology
- PEFRs, spirometry, methacholine responsiveness, SIC – changes related to work

Immunologic tests (IgE antibodies, skin prick)
*** The more positive findings the more certain the relationship to work*
Best to complete evaluation and/or refer to specialist before removing patient from work

Work-related Asthma

Asthma but not Work-related Asthma

Decide if primary Occupational Asthma (Sensitizer or Irritant) based on above

Yes → **Occupational Asthma**

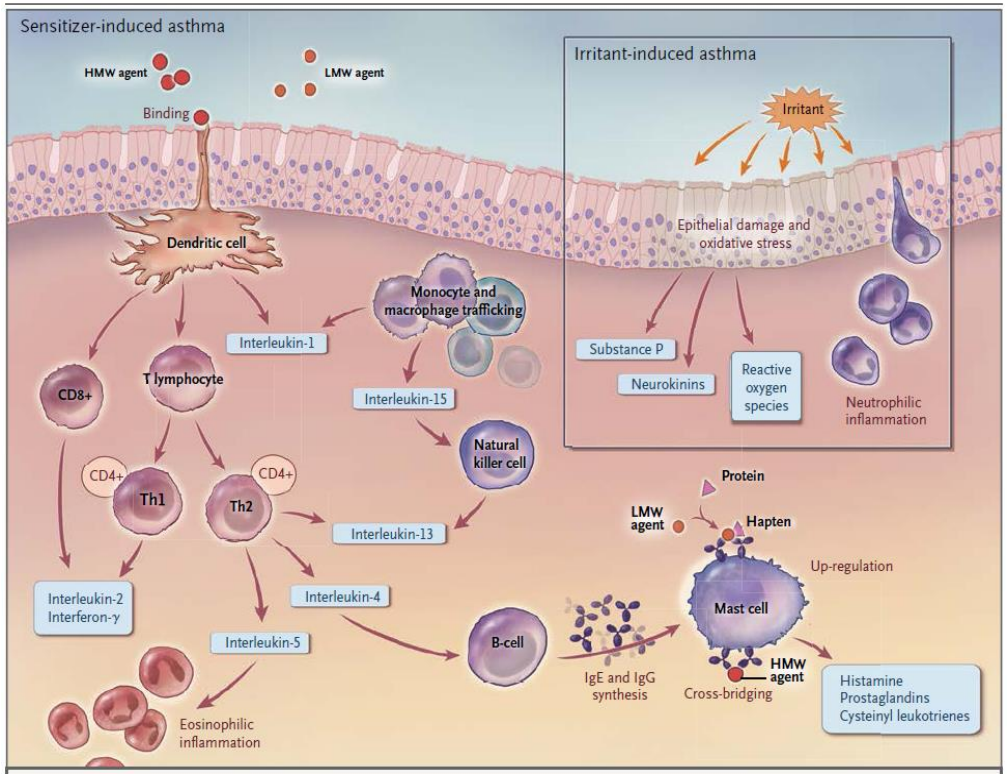
No → **Work-exacerbated Asthma**

Management OA
A) Sensitizer
- Avoid sensitizer exposures
- Consider reduction exposure and/or immunotherapy in selected situations
- Surveillance of exposed workers

B) Irritant
- Reduce irritant exposures

Both:
- Optimize medical treatment asthma
- Monitor patient - Job change if severe/worse asthma
- Assist with compensation
- Consider prevention for other exposed workers

Management WEA
Optimize medical treatment asthma
Reduce workplace and non-work triggers
Monitor patient - job change if severe / worse asthma
Consider compensation
Consider prevention for other exposed workers



CHEST 2011; 139(3):674–681

N Engl J Med 2014;370:640-9.

Table 3. Prevention of Sensitizer-Induced Occupational Asthma.

Primary prevention

Avoid introducing predicted new sensitizing agents into the workplace (efficacy as primary prevention currently theoretical).

Avoid use of known sensitizing agents if safer alternatives are available.

Modify the physical or chemical form of known sensitizers to reduce risk of exposure (e.g., less volatile preparations, gloves with a low-protein and low-powde

Reduce exposure to work sensitizers by mea measures (e.g., use of robotics, containm

Educate workers in the use of safe practices

Monitor and control levels of exposure to wo

Secondary prevention (early detection)

Institute medical-surveillance programs for workers at risk, consisting of preplacement and periodic respiratory questionnaires, with spirometry and immunologic tests as indicated.

Ensure that health care providers have adequate knowledge of occupational asthma and consider it early in the evaluation of all adults with asthma symptoms, leading to early diagnosis and management of occupational asthma.

Educate workers about the risks of occupational asthma through workplace programs, information provided by health care providers, and public-education programs (e.g., from news media, lung associations, and Web-based programs).

Tertiary prevention (appropriate treatment)

Evaluate symptomatic workers early and obtain an accurate diagnosis.

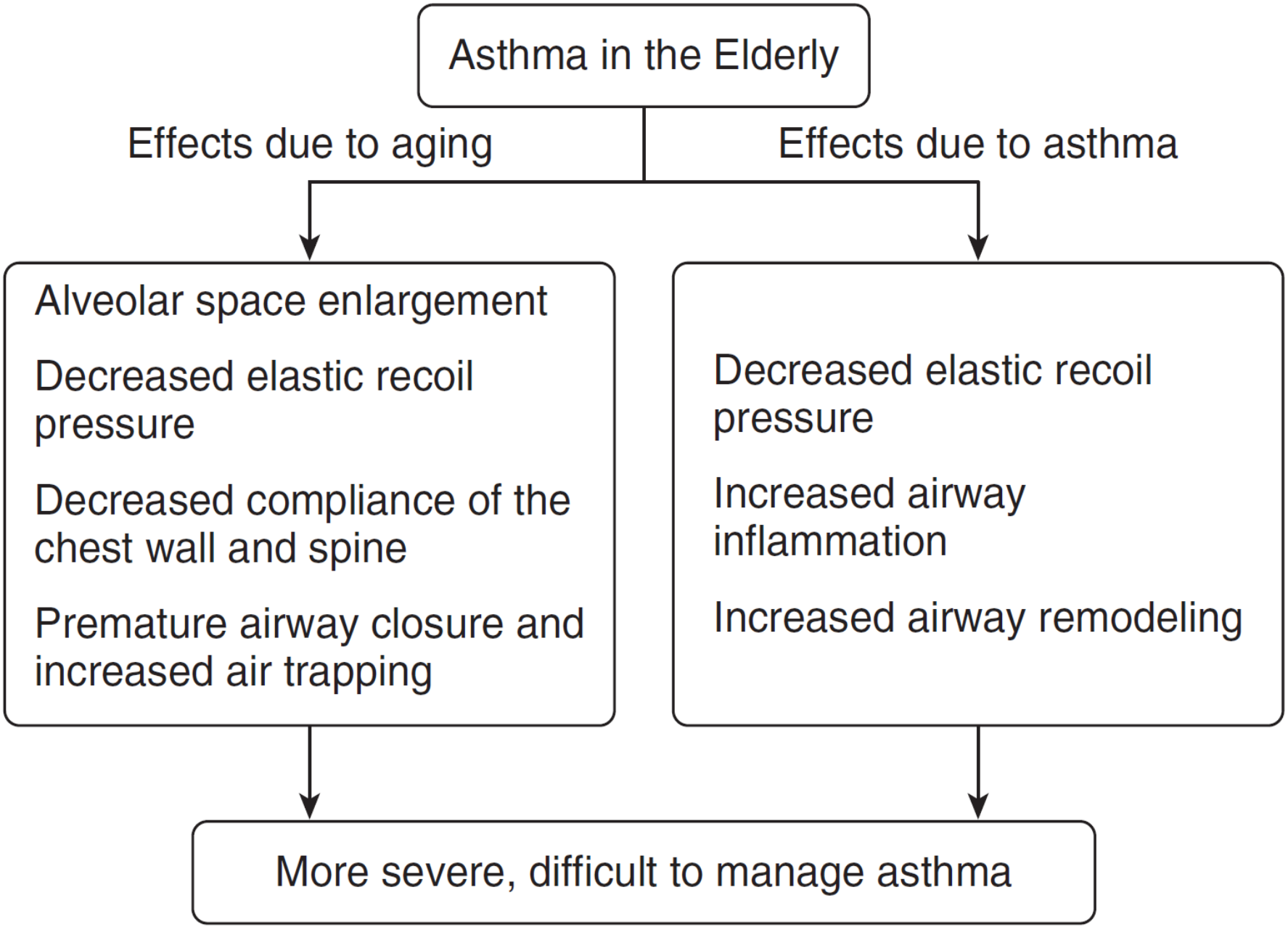
Remove workers from further exposure to the implicated agent after a confirmed diagnosis, when possible.

Control other triggers and use pharmacologic measures if necessary.

Assist the patient with a workers' compensation claim when applicable, to limit the socioeconomic effects of the diagnosis.

Monitor the patient's asthma in future work locations to ensure safe placement.

N Engl J Med 2014;370:640-9.

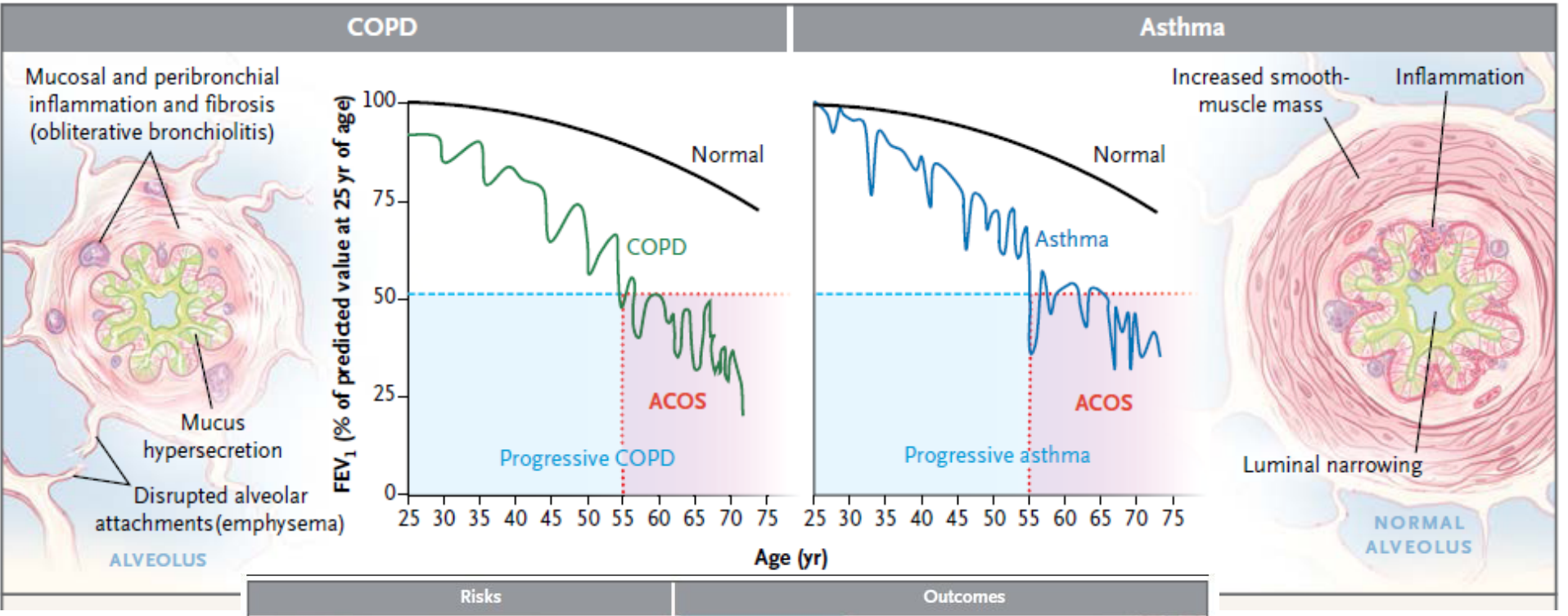


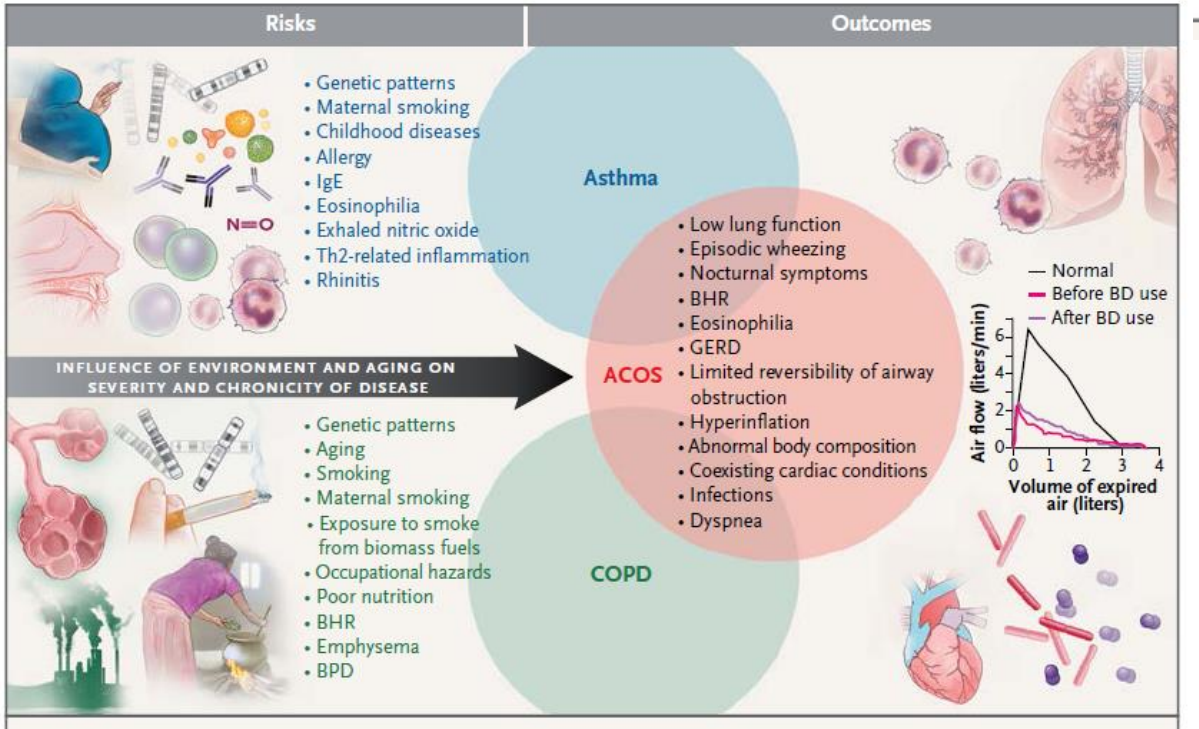
Ann Am Thorac Soc Vol 13, No 11, pp 2064–2077, Nov 2016

Diagnostic and treatment comparison of elderly and younger patients with asthma

Test/Characteristic	Elderly	Young
Spirometry	May be less useful in frail patients; reference standards not widely available	Generally useful tool to assess asthma severity
Bronchodilator responsiveness	May be less pronounced	Variable but generally greater
eNO	May be useful	May be useful
Methacholine challenge	Less often used because of more frequent contraindications (e.g., cardiovascular disease)	Useful; overall fewer contraindications
Atopy	Less common	Common
Comorbidities	COPD, heart disease more common	Allergic rhinitis more common
Phenotypes	Limited knowledge, but late-onset asthma, long-standing asthma, and ACOS described	Multiple phenotypes described
Sputum cellularity	Generally more neutrophilic	Generally more eosinophilic
Therapy	No age-specific guidelines Optimal regimen unknown More susceptible to adverse effects due to comorbidities, drug-to-drug interactions, and polypharmacy Inability to use certain inhalers due to lack of dexterity and reduced inspiratory flow	Guideline-specific regimens in place that address the needs of most patients

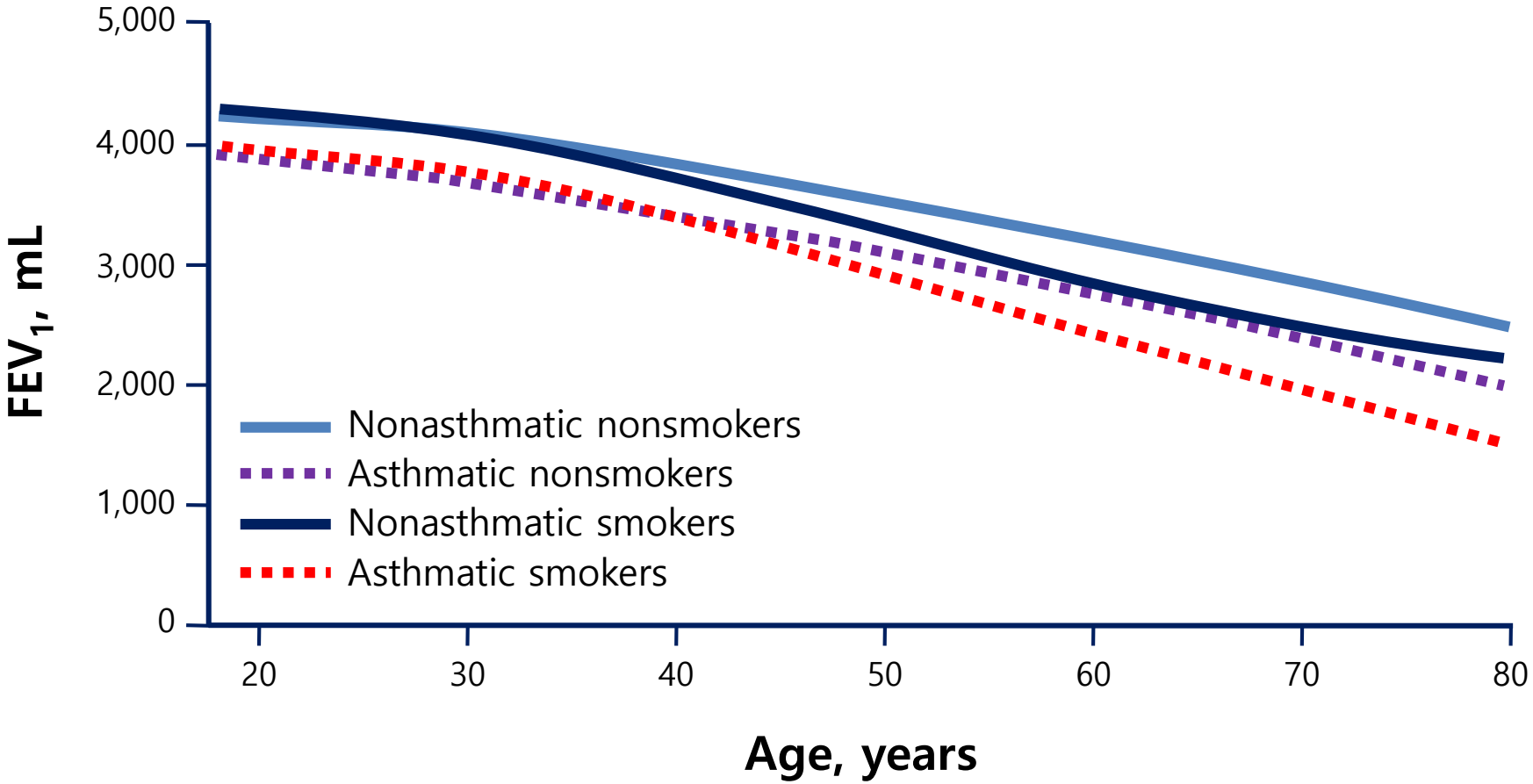
Definition of abbreviations: ACOS = asthma–COPD overlap syndrome; COPD = chronic obstructive pulmonary disease; eNO = exhaled nitric oxide.


COPD
Asthma
Mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis)
Mucus hypersecretion
Disrupted alveolar attachments (emphysema)
ALVEOLUS
FEV1 (% of predicted value at 25 yr of age)
100
75
50
25
0
Normal
COPD
ACOS
Progressive COPD
Normal
Asthma
ACOS
Progressive asthma
25 30 35 40 45 50 55 60 65 70 75
Age (yr)
Increased smooth-muscle mass
Inflammation
Luminal narrowing
NORMAL ALVEOLUS

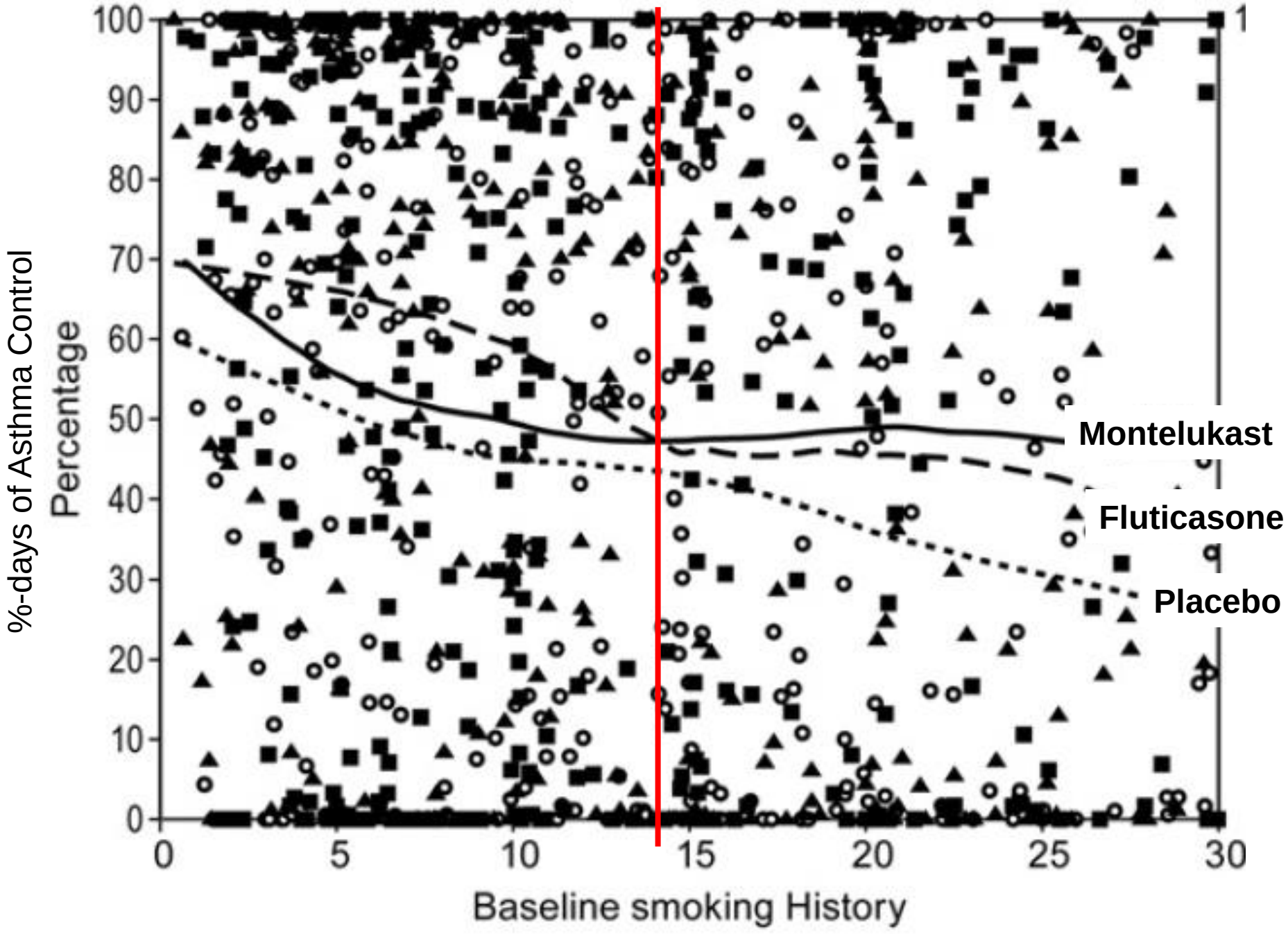

Risks
Outcomes
• Genetic patterns
• Maternal smoking
• Childhood diseases
• Allergy
• IgE
• Eosinophilia
• Exhaled nitric oxide
• Th2-related inflammation
• Rhinitis
N=O
Asthma
INFLUENCE OF ENVIRONMENT AND AGING ON SEVERITY AND CHRONICITY OF DISEASE
ACOS
• Low lung function
• Episodic wheezing
• Nocturnal symptoms
• BHR
• Eosinophilia
• GERD
• Limited reversibility of airway obstruction
• Hyperinflation
• Abnormal body composition
• Coexisting cardiac conditions
• Infections
• Dyspnea
• Genetic patterns
• Aging
• Smoking
• Maternal smoking
• Exposure to smoke from biomass fuels
• Occupational hazards
• Poor nutrition
• BHR
• Emphysema
• BPD
COPD
Normal
Before BD use
After BD use
Air flow (liters/min)
Volume of expired air (liters)

Impact of smoking on lung function in asthmatic smokers

Mean FEV_1 Among Men Aged 18 to 80 Years (Australia—1966–1995)



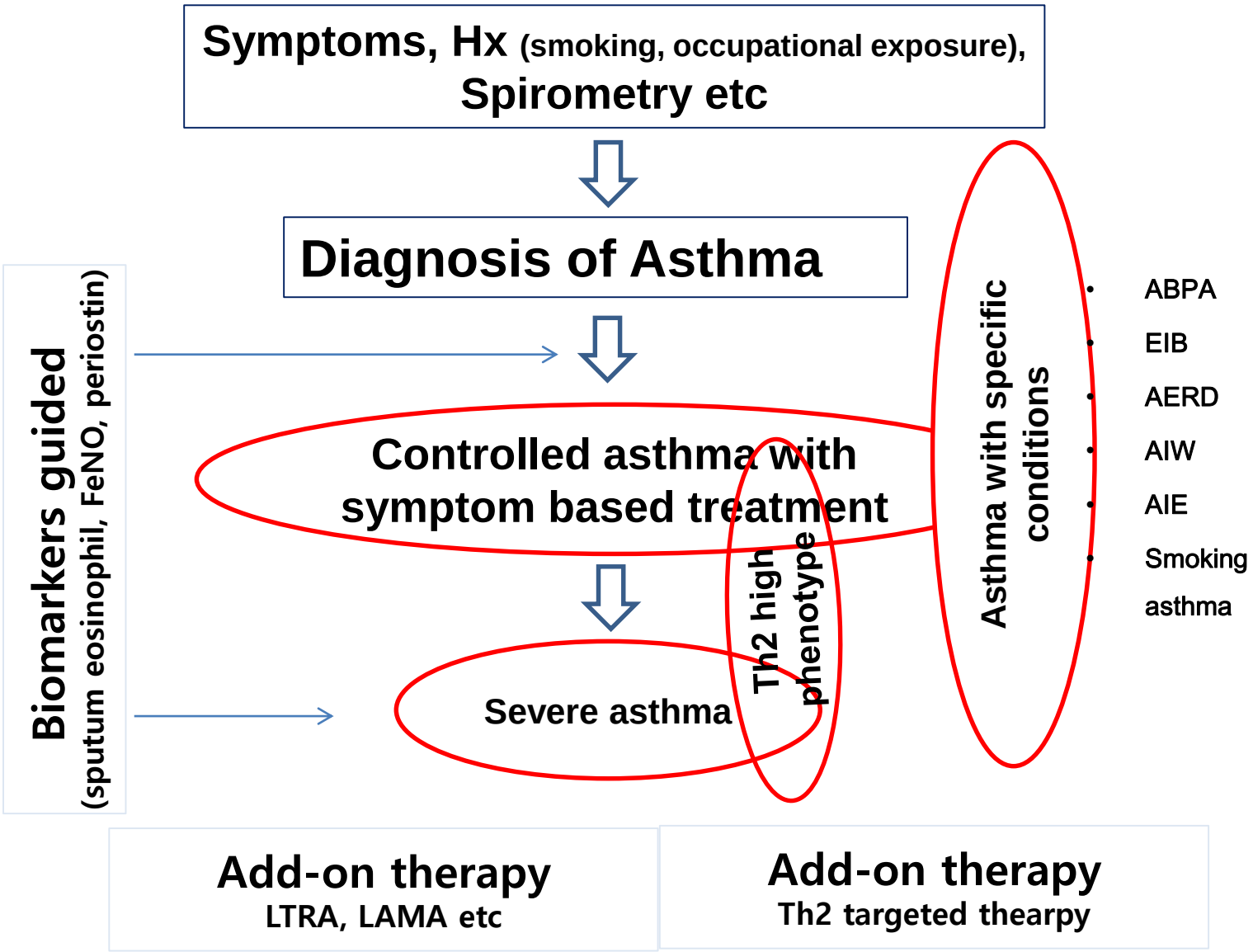
Am J Respir Crit Care Med. 2005;171:109–114.


%-days of Asthma Control
Percentage
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Baseline smoking History
Montelukast
Fluticasone
Placebo

Asthma phenotypes with specific conditions impacting on diagnosis and treatment of BA

- ABPA
  - High dose steroids
  - Anti-fungal agents
- AERD
  - Diagnostic aspirin challenge
  - avoid all cyclooxygenase-1 (COX-1)-inhibiting NSAIDS
  - LTRA
  - Aspirin desensitization
- Asthma in workplace (AIW)
  - Work history and other exposures
  - Avoidance of occupational exposure
  - Identification and elimiination of occupational sensitizer
- Asthma in Elderly (AIE)
  - Commorbidities, cognitive impairment
  - ACOS
- Smoking asthma
  - Smoking cessation
  - Higher dose of ICS
  - LTRA
  - LAMA
  - Fine particled inhalers?

Clinically relevant phenotypes/endotypes?



Summary

- Phenotyping/endotyping
  - Development of tailored medicine
  - Further understanding pathophysiology
  - New targeted therapy
- In current clinical situation,
  - limited number of therapeutic tools for asthma and lack of simple and consistent biomarkers for identifying specific phenotypes
  - Approaches to find the phenotypes and indications appropriate to current medications are necessary
- Majority of patients with asthma will be responsive to ICS based treatment for controlling symptoms and reducing future risk.
- Nevertheless, physician should try to find some phenotypes of asthma which require special diagnostic process and are expecting for additional therapeutic gains by applying specific treatment strategies
  - ABPA, Asthma in working place, AERD, smoking asthmatics etc.
- New medications targeting Th2 inflammation may be beneficial in asthma with high activity of Th2 cascades including severe asthma and biomarker-guided treatment may be necessary.

Thank you for your attention!