Practising Personalized Medicine

Asthma: are we already there?

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CONTENTS

Bronchial Asthma

- Initially asthma was considered to be an allergic, eosinophilic, and Th2-mediated disease that was responsive to corticosteroids
- The pathophysiology of asthma is very complex and includes several disease variants.
- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation with variable expiratory airflow limitation.

GINA guideline

- The term 'asthma' equates to a definition of grouped clinical and physiological characteristics. These characteristics could identify syndromes, phenotypes, or even multiple diseases rather than a single disease.

Asthma Syndrome

Clinical

- Age of the onset
- Gender, race
- Asthma in smokers
- Premenstrual asthma
- Exercise-induced asthma
- Professional asthma
- Associated comorbidities
  - Atopy, GERD, rhinitis, obesity, food allergy, aspirin-sensitivity

Physiologic

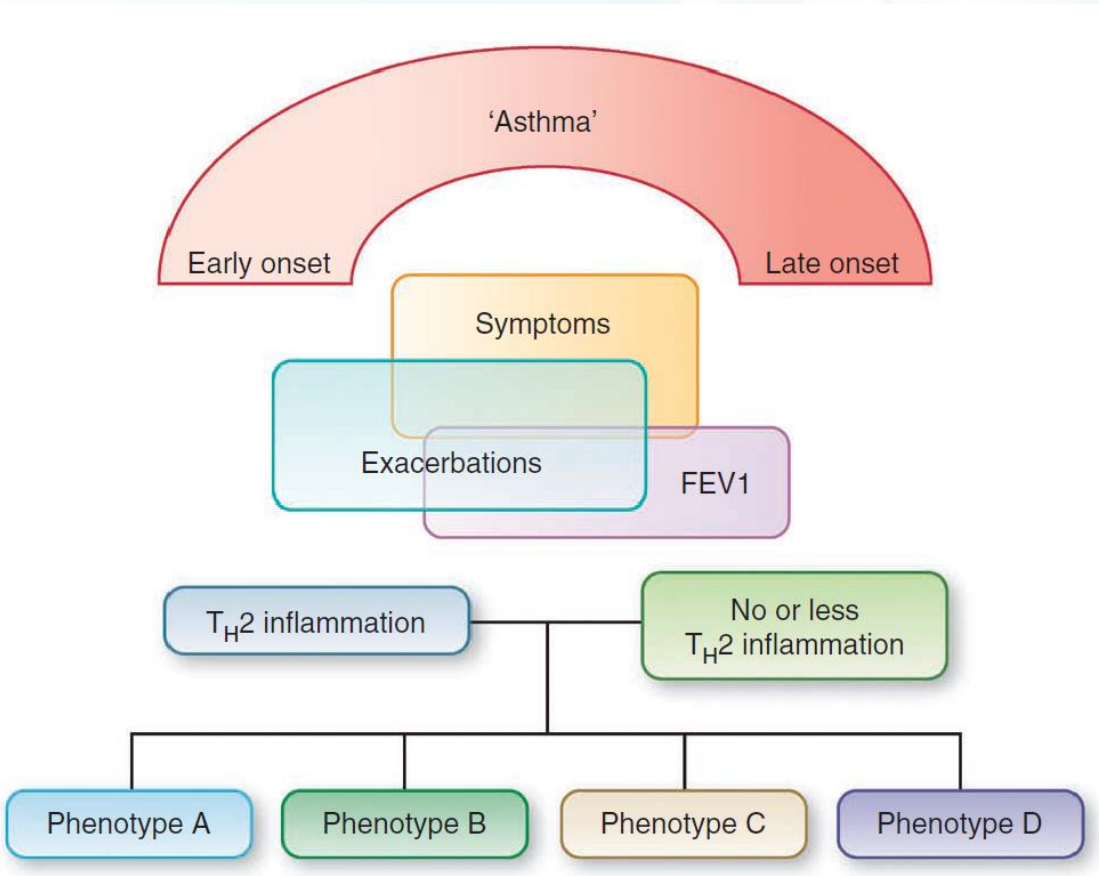
- Low FEV1
- Fixed airway obstruction
- Highly collapsible airways
- Fast decline in lung function

Pathologic

- Eosinophilic
- Neutrophilic
- Mixed
- Pauci-granulocytic
- Airway remodeling

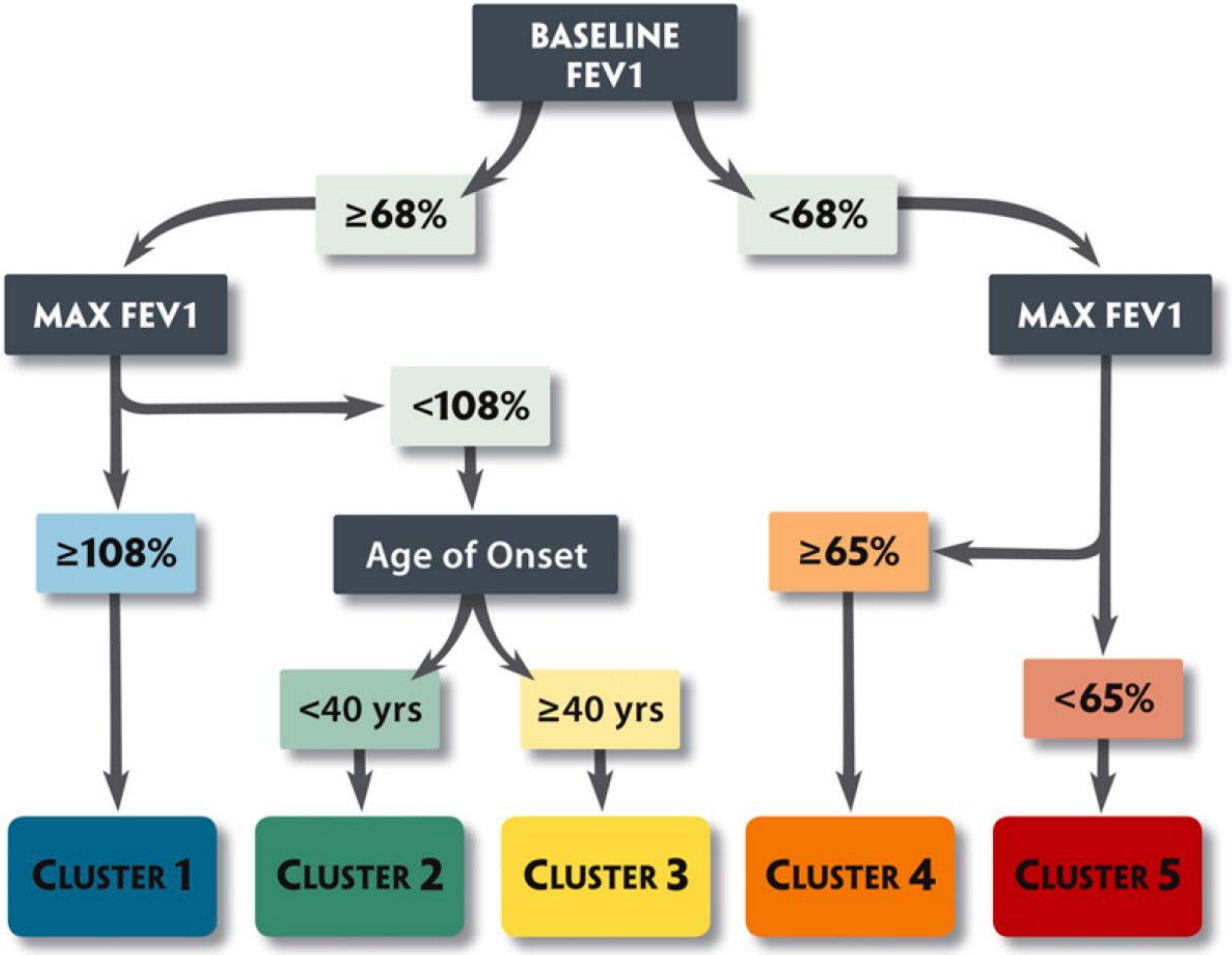
Phenotypes of Asthma

- **Phenotype:** a term used to define the clinically observable characteristics



Wenzel SE. Nat Med 2012;12:716-25

Phenotypes of Asthma

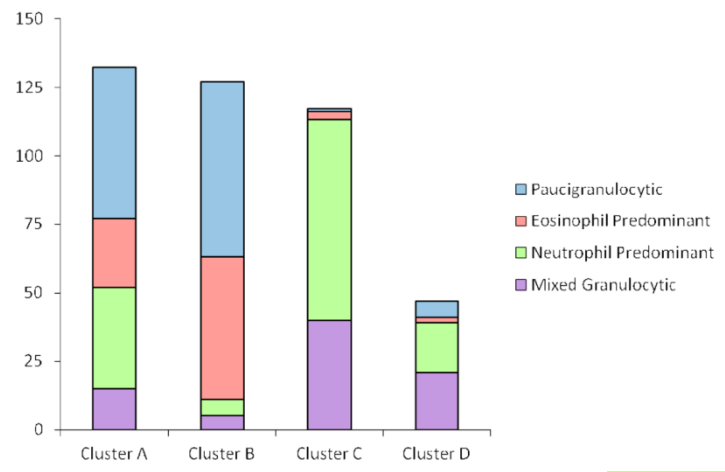


Moore WC, et al. Am J Respir Crit Care Med 2010;181:315-23

Asthma Phenotypes

	Asthma Phenotypes Identified at Baseline*						
	Phenotype A: "Allergic, Few Symptoms, No Treatment"	Phenotype B: "Nonallergic, Few Symptoms, No Treatment"	Phenotype C: "Nonallergic, High Symptoms, Treatment"	Phenotype D: "Allergic, High Symptoms, Treatment, BHR"	Phenotype E: "Allergic, Moderate Symptoms, BHR"	Phenotype F: "Allergic, Moderate Symptoms, Normal Lung Function"	Phenotype G: "Nonallergic, Moderate Symptoms, No Treatment"
Exacerbation reported at follow-up							
% (*n*)†	4.9 (20)	5.0 (16)	20.0 (40)	17.5 (85)	9.5 (21)	9.2 (28)	14.0 (37)
OR (95% CI)	0.98 (0.5–1.93)	1 (—)	4.75 (2.58–8.74)	4.02 (2.31–7.01)	2.04 (1.02–3.93)	1.93 (1.02–3.65)	3.10 (1.68–5.7)

Boudier A, et al. Am J Respir Crit Care Med 2013;188:550-60



- A. Early-onset atopic asthma, female, and normal lung function, younger subjects
- B. Early-onset atopic asthma, eosinophil predominate, slightly older mostly female, with more medication use, normal or reversible PFT
- C. Older obese women, late-onset, less likely atopic with decreased PFT, neutrophil inflammation, highly symptomatic
- D. More severe asthma with high medication requirements, higher proportion of men, most are obese, late onset, markedly reduced lung function with persistent airflow obstruction

Moore WC, et al, J Allergy Clin Immunol 2014;133:1557-63

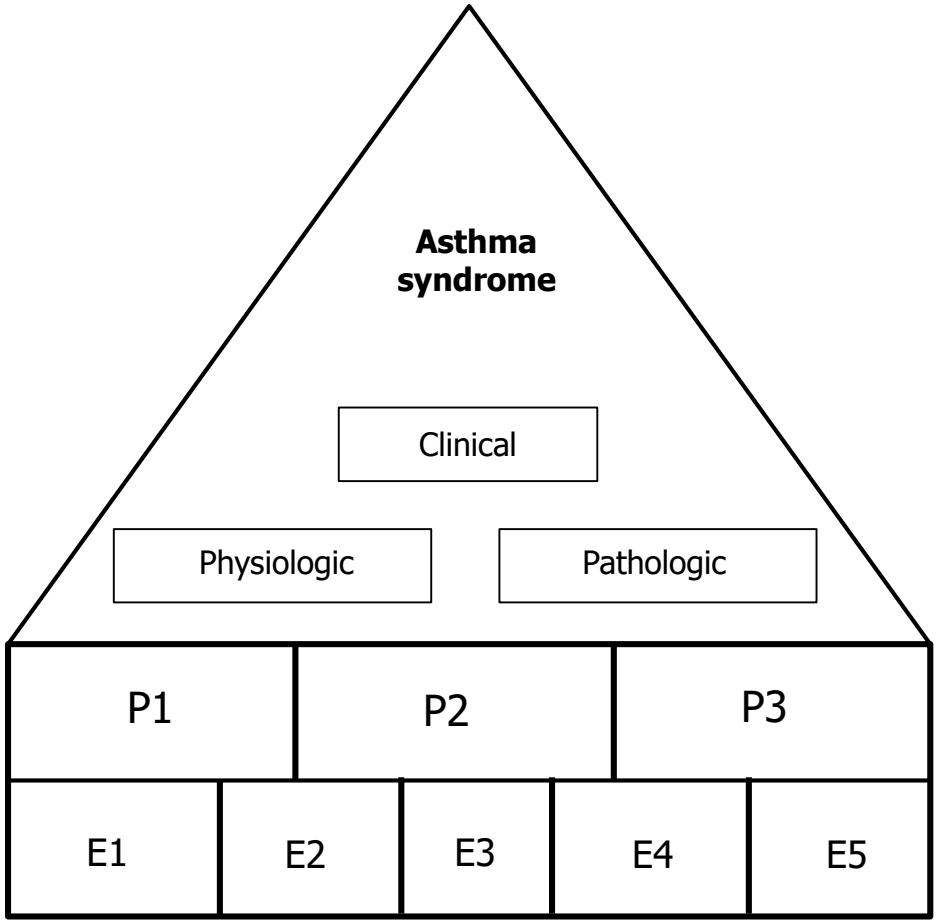
Asthma Phenotypes

- Identification of asthma phenotypes, which elucidate clinically observable characteristics, may help characterize the disease and predict most appropriate treatment.
- Treating asthma based on phenotypes with no direct relationship to the disease mechanisms is suboptimal, given the variability in treatment response.

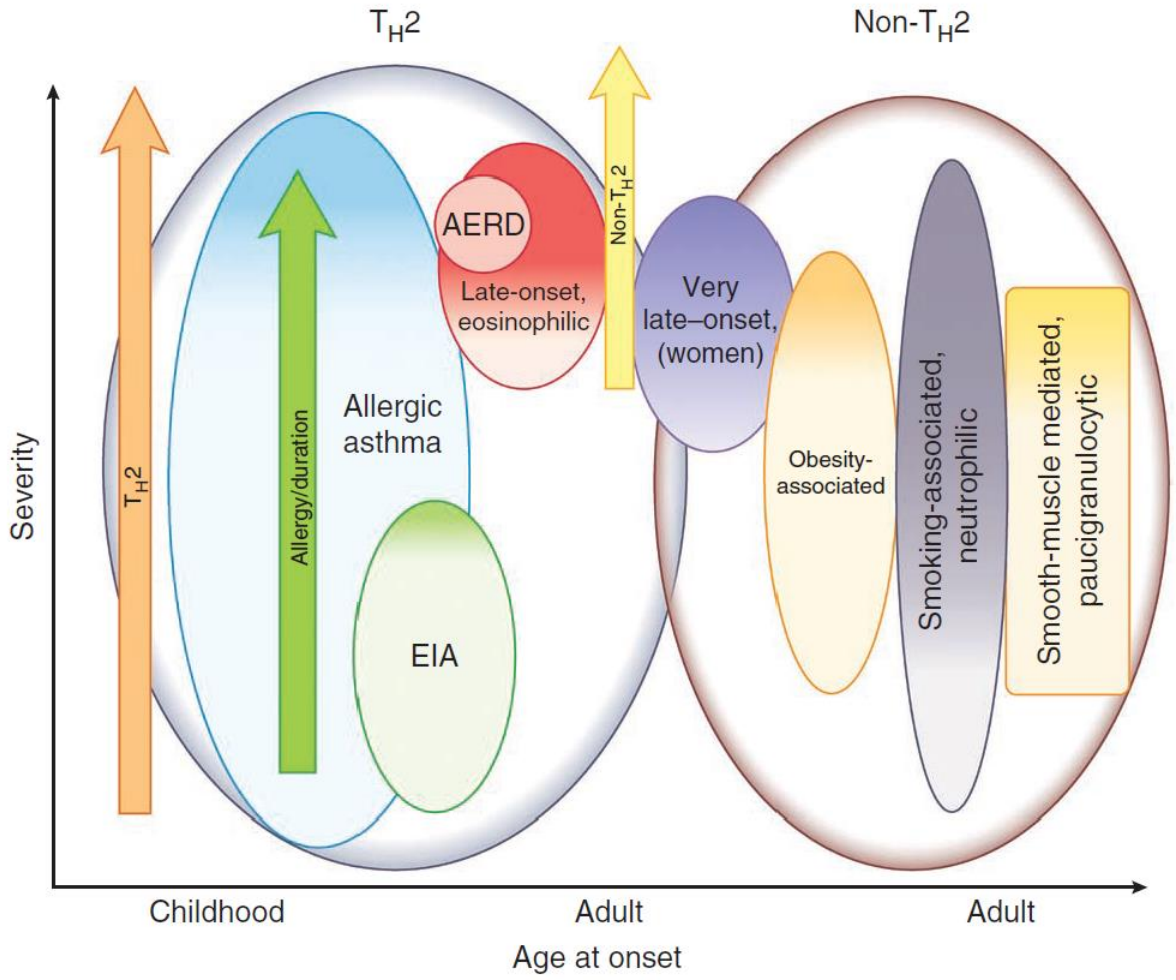
- The term endotype can be introduced to describe distinct subtypes with a defining etiology and consistent pathobiologic mechanisms.
- A key goal in understanding endotypes is the identification of proposed biomarkers that will allow the prediction of response to targeted therapy.

Hierarchy of Asthma Phenotypes and Endotypes

Asthma syndrome and its phenotypes and endotypes

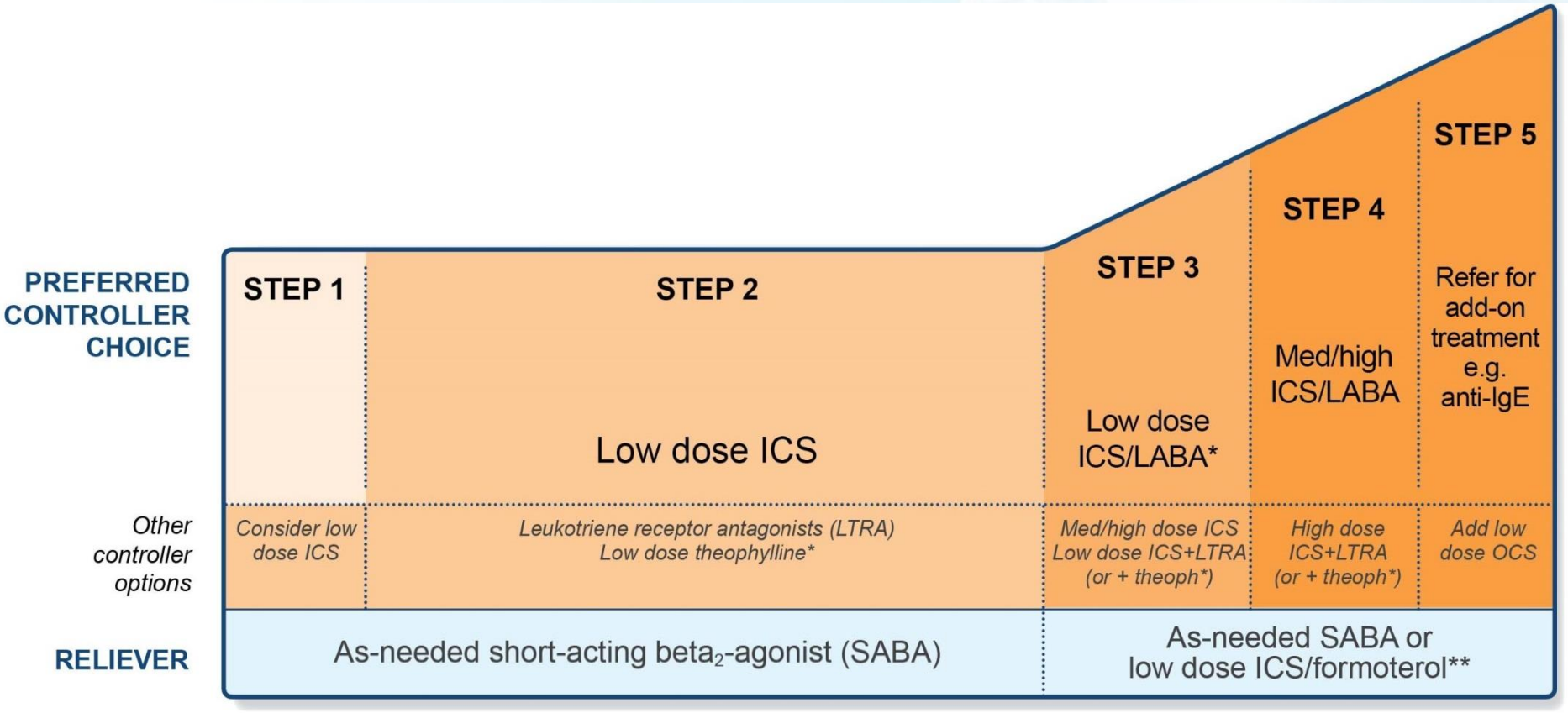


Asthma Phenotypes and Endotypes



Wenzel SE. Nat Med 2012;12:716-25

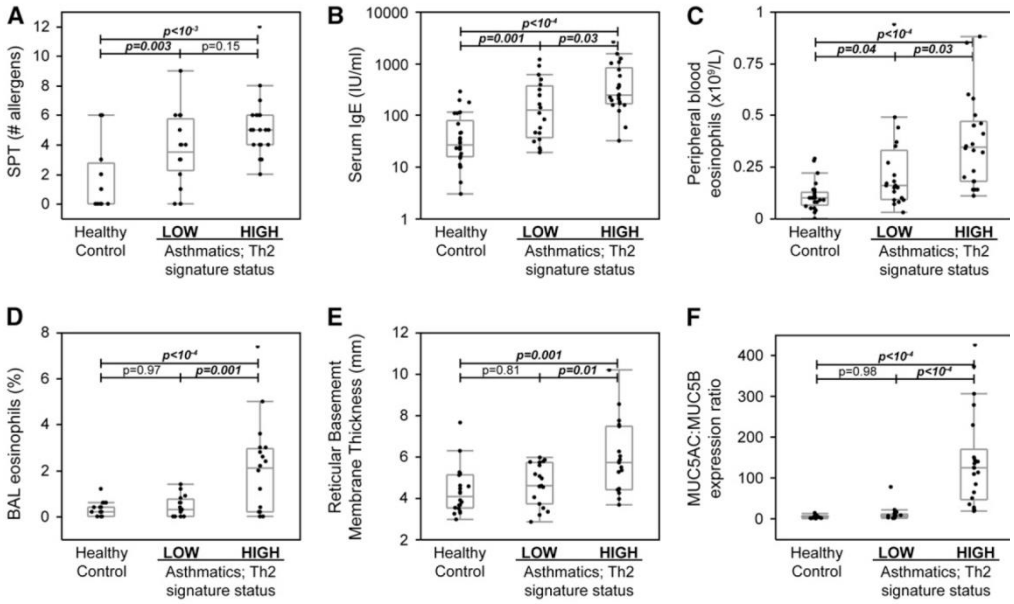
Asthma Treatment in GINA

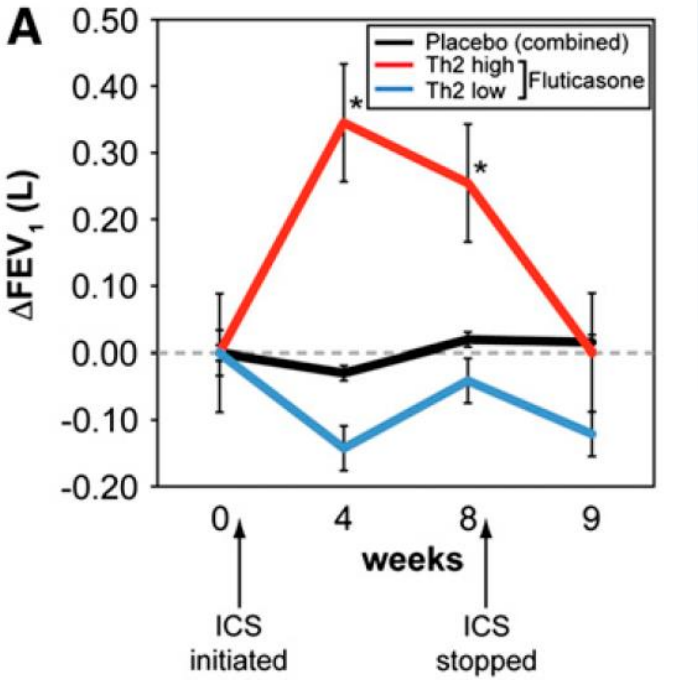


*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Potential Implications for Therapy

- A ‘Th2-high’ identifies patients with high eosinophilia and good therapeutic response to corticosterids.

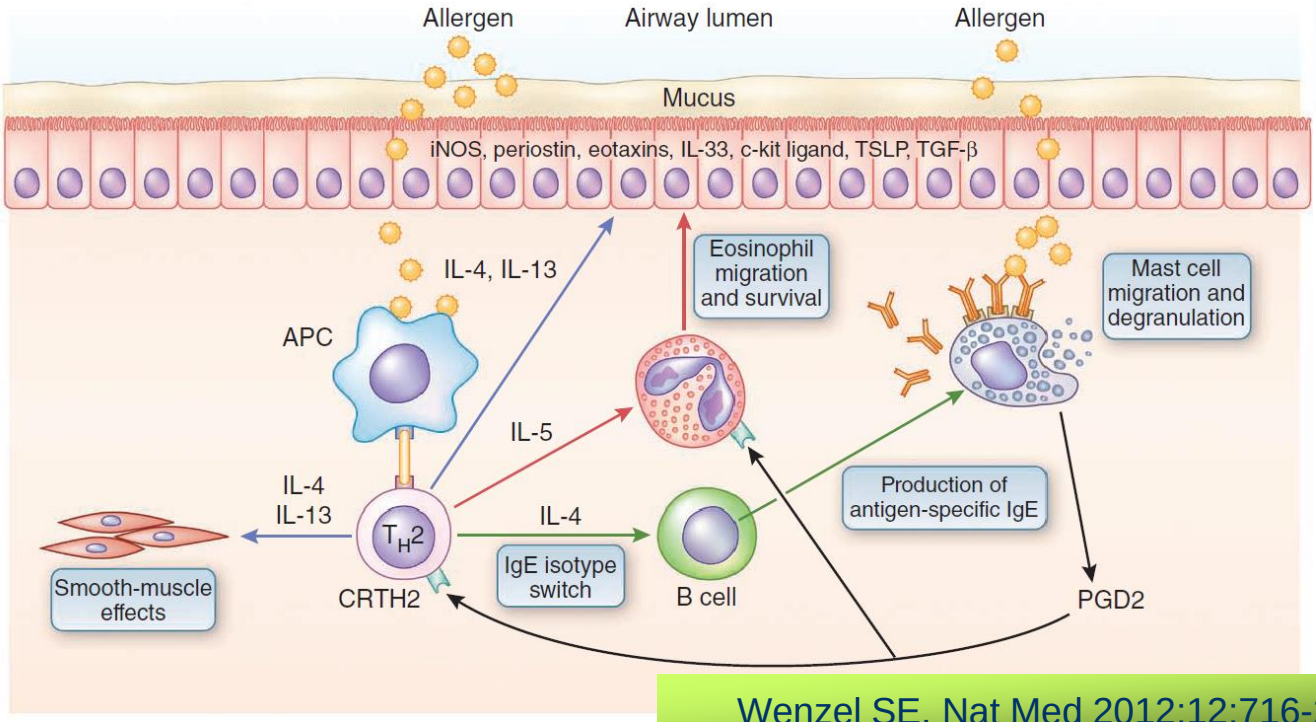




Woodruff PG, et al. Am J Respir Crit Care Med 2009;180:388-95

Th2-Associated Asthma

- A ‘Th2-high’ identifies patients with high eosinophilia and good therapeutic response to corticosterids.
  - Early-onset allergic asthma
  - Late-onset persistent eosinophilic asthma
  - Exercise-induced asthma



Wenzel SE. Nat Med 2012;12:716-25

Th2-Associated Early-Onset Allergic Asthma

- with childhood onset and a history of allergy or atopy
- commonly have a family history of asthma
- Genetics
  - Higher numbers of mutations in Th2 related genes (IL4, IL13, IL4Rα) associated with greater severity of disease
- Biomarkers
  - Positive SPT
  - elevated IgE
  - Sputum eosinophils (≥2% sputum inflammatory cells)
  - High FeNO (usually 30-35 parts per billion or higher)
  - Th2 cytokines IL-4, IL-5, IL-9, IL-13, and periostin measured in sputum, BAL, serum, and bronchial biopsy

Wenzel SE. Nat Med 2012;12:716-25

Th2-Associated Early-Onset Allergic Asthma

Treatment response

- Well response to corticosteroid

- Th2 targeted therapy
  - Anti-IgE (omalizumab) in severe asthma
  - Anti-IL-13 (lebrikizumab) :

    Surrogate marker predicting better response is high serum levels of periostin.

Scheerens H , et al,. J Allergy Clin Immunol 2011;127:AB164

  - Inhaled IL-4Rα antagonist (Pitrakinra)

    Surrogate marker predicting better response is *IL4RA* polymorphism.

Slager RE , et al,. J Allergy Clin Immunol 2010;126:875-8

Wenzel SE. Nat Med 2012;12:716-25

Th2-Associated Late-Onset Persistent Eosinophilic Asthma

- adult-onset, often severe
- less allergic form than early-onset asthma
- Family history is rare
- Aspirin-exacerbated airway disease (AERD) is thought to be a subset of this subtype.
- Biomarkers
  - Lung eosinophilia:

    persistent sputum eosinophilia ≥2% despite corticosteroid therapy
  - Th2 process differs from and is more complex than the one associated with the early-onset allergic phenotype
  - Some individuals show sputum neutrophilia intermixed with their eosinophilic process.

Wenzel SE. Nat Med 2012;12:716-25

Th2-Associated Late-Onset Persistent Eosinophilic Asthma

Treatment response

- requires high-dose cortocosteroids to overcome the refractoriness

- IL-4 and IL-13 targeted therapy
- IL-5 targeted therapy (Mepolizumab)
  - Much better efficacy in this endotype

    (as IL-5 dependent eosinophilia may be more important)
  - The amount of remaining Th2 inflammation than on the previously used clinical characteristics

Wenzel SE. Nat Med 2012;12:716-25

Aspirin-exacerbated airway disease (AERD)

- AERD is associated with sinusitis, nasal polys, and non-IgE-mediated responses to aspirin and other COX-1 inhibitors

- Biomarkers
  - cysteinyl leukotriene (LT) pathway is upregulated
- Genetics
  - LT-related gene polymorphysm

- Treatment response
  - LT modifiers can have a robust impact

Wenzel SE. Nat Med 2012;12:716-25

Exercise-Induced Asthma (EIA)

- Symptoms occur primarily after exercise
- Consistent with a relationship to Th2 processes, EIA may be associated with high percentages of eosinophils in both sputum and tissue.
- No distinct genetic factors or biomarkers

Treatment response

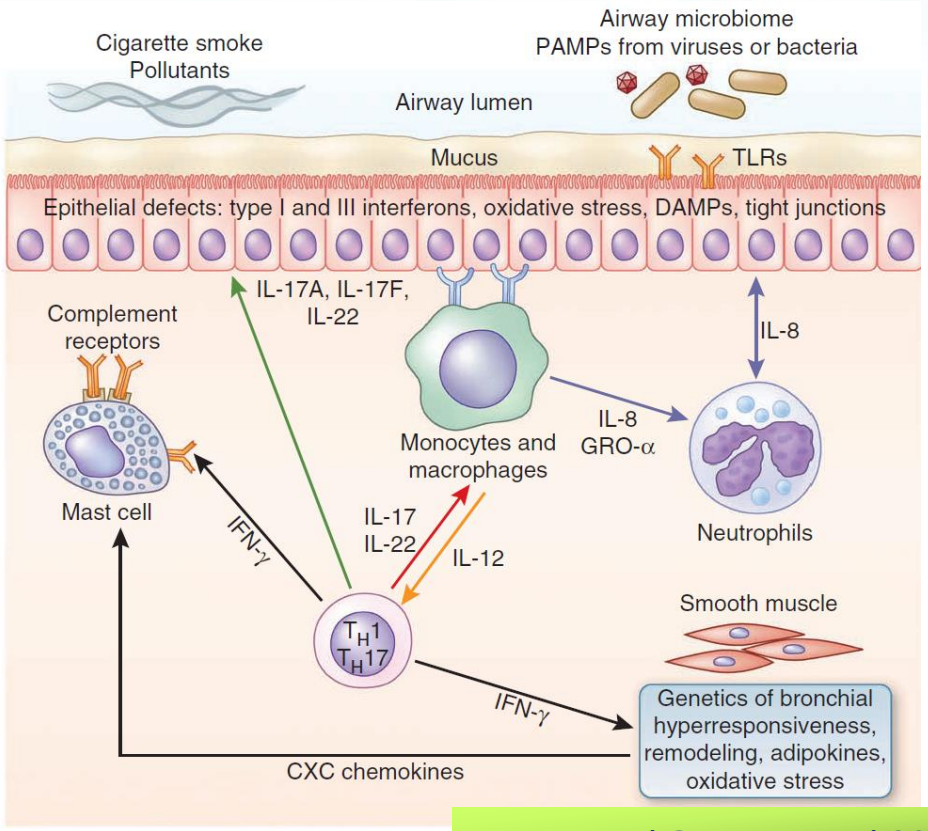
- LT modifiers
  - high LTE4/FeNO ratio is surrogate marker predicting better response
- IL-9 targeted therapy

Parker JM et al. BMC Pulm Med 2011;11:14

Wenzel SE. Nat Med 2012;12:716-25

Non Th2-Associated Asthma

- The lack of efficacy of Th2 targeted therapy
- Little is understood about its related molecular elements.
  - Obesity-related asthma
  - Neutrophilic asthma



Wenzel SE. Nat Med 2012;12:716-25

Obesity-Related Asthma

- generally women with late-onset (mid-40s), minimally allergic asthma with a high burden of symptoms
- Biomarkers
  - No specific biomarkers
  - High expression of non-Th2 mediators such as TNF-α, IL-6
  - Hormones of obesity, such as adiponectin, leptin, and resistin
  - Increased oxidative stress

Treatment response

- responds relatively poorly to corticosteroids
- Weight loss as a therapy seems to be more beneficial when the asthma is not associated with Th2 inflammation

Wenzel SE. Nat Med 2012;12:716-25

Neutrophilic Asthma

- A unique form of asthma?
  - A different stage of severity
  - Persistent bacterial colonization or infection on the background of a previously eosinophilic asthma
- Characterized by (fixed) airflow limitation,

  more air trapping, thicker airway walls (in CT)
- Mechanisms
  - Novel mechanisms involve the activation of innate immune responses with a possible role of bacteria, viruses.
  - Th17 immunity
- Biomarkers
  - IL-17A, IL-17F
  - IL-8, IL-32, IL-1, TNF-α

Wenzel SE. Nat Med 2012;12:716-25

Neutrophilic Asthma

Treatment response

- Corticosteroids are less effective
- Macrolide antibiotics may have some efficacy
  - Whether the treatment response was caused by the antibiotic or anti-inflammatory effects of macrolides is not clear.
- IL-17 targeted therapy
  - Awaits evidence from ongoing clinical trials

Wenzel SE. Nat Med 2012;12:716-25

Smoking Asthma

- It is unknown if smoking asthma is a subtype of neutrophilic asthma or an independent endotype.
  - Since not all smoking asthma is accompanied by neutrophilia, it is more likely that there is only a partial overlap between neutrophilic asthma and smoking asthma.
- Little is understood regarding the genetics or biomarkers
  - FeNO levels are decreased by smoking

Treatment response

- Quitting smoking

Wenzel SE. Nat Med 2012;12:716-25

Treatment Response of Asthma Phenotypes

Phenotype	Responsive to therapy
Early-onset allergic	Corticosteroid, Anti-IgE, Th2 targeted: anti-IL-13, IL-4Rα antagonist
Late-onset eosinophilic	Anti-IL-5
Exercise-induced	Cysteinyl LT modifiers, anti-IL-9
Obesity-related	Weight loss, antioxidants
Neutrophilic	Macrolide antibiotics
Smoking	Quitting smoking
ABPM	Anti-IgE, oral steroids, anti-fungal agent
Extensive airway remodeling (ie, severe refractory)	Bronchial thermoplasty

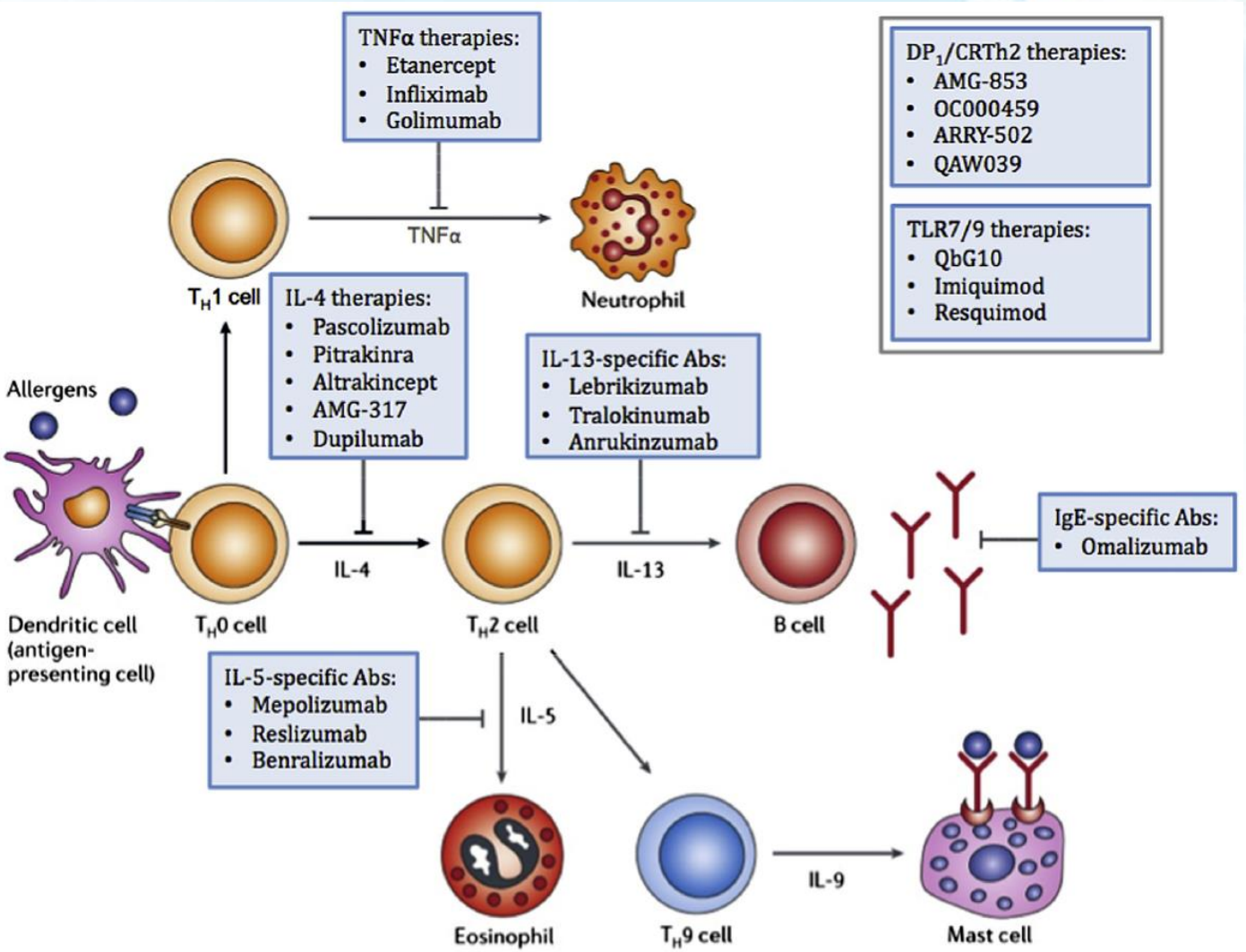
Wenzel SE. Nat Med 2012;12:716-25

1 Phenotype and Endotype

2 Treatment Effects in Phenotype

3 Marker to Assess Treatment Effects

Biologic Therapy for Asthma



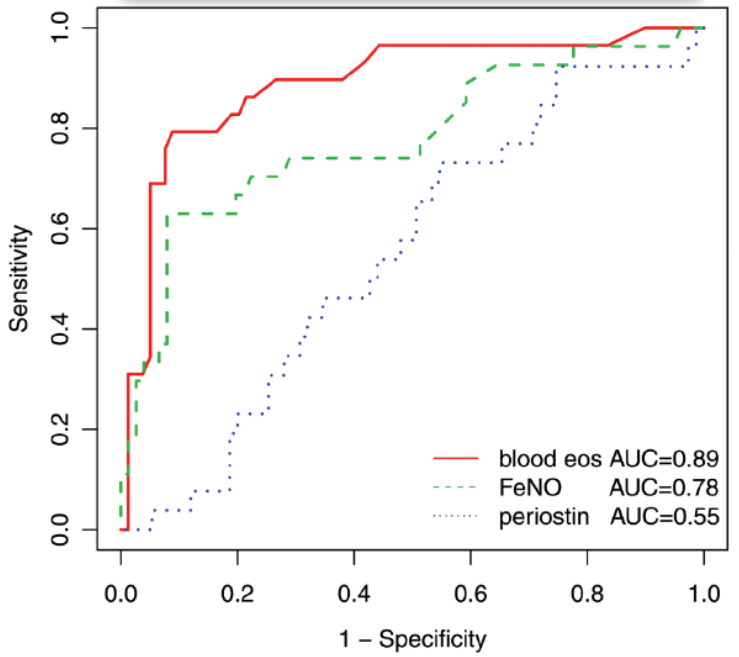
Bice JB, et al. Ann Alelrgy Asthma Immunol 2014;112:108-15

Asthma Biomarkers used in Biologic Trials

Biomarker	Strengths	Waekness
Total IgE	Easy to obtain, inexpensive, sensitive	Not specific for all asthma types
Specific IgE	Easy to obtain, inexpensive, good correlation with atopic asthma	Not specific for all asthma types
FeNo	Easy to obtain, correlation with airway eosinophilic inflammation and IL-13 production	Expensive, not specific for all asthma types
Sputum eosinophils	Correlation with airway eosinophilic inflammation, decreased FEV1, and increased BHR	Difficult to obtain
Blood eosinophils	Inexpensive, easy to obtain, Responds to multiple therapies	Not sensitive or specific for asthma or atopy
Serum periostin	Sensitive indicator of Th2 airway inflammation	Expensive, not readily available

Diagnostic Accuracy for Eosinophilic Airway Inflammation

External validation cohort



	Blood Eo	FE_{NO}	Periostin
ROC AUC	89%	78%	55%
95% CI	0.81-0.96	0.66-0.89	0.43-0.67
P value	<0.001	<0.001	0.44

Table 2 Sensitivity, specificity, PPV and NPV of different surrogate markers using alternative cut-points to diagnose eosinophilic airway inflammation (less than, more than or equal to 3% sputum eosinophils)

	Threshold	Sensitivity	Specificity	PPV	NPV
Blood eosinophils	>0.22×10^9/L	86	79	60	93
Blood eosinophils	≥0.25×10^9/L	79	84	64	91
Blood eosinophils	≥0.27×10^9/L	78	91	79	91
FE_{NO} level	>20 ppb	74	57	40	87
FE_{NO} level	≥24 ppb	74	63	42	87
FE_{NO} level	≥42 ppb	63	92	74	89
FE_{NO} level	>50 ppb	56	92	67	84
Serum periostin (in-house)	>26 ng/mL	54	57	29	77

NPV, negative predictive value; PPV, positive predictive value.

Wagener AH, et al. Thorax 2015;70:115-20

Periostin as a Biomarker of Eosinophilic Airway Inflammation

- 67 patients with asthma

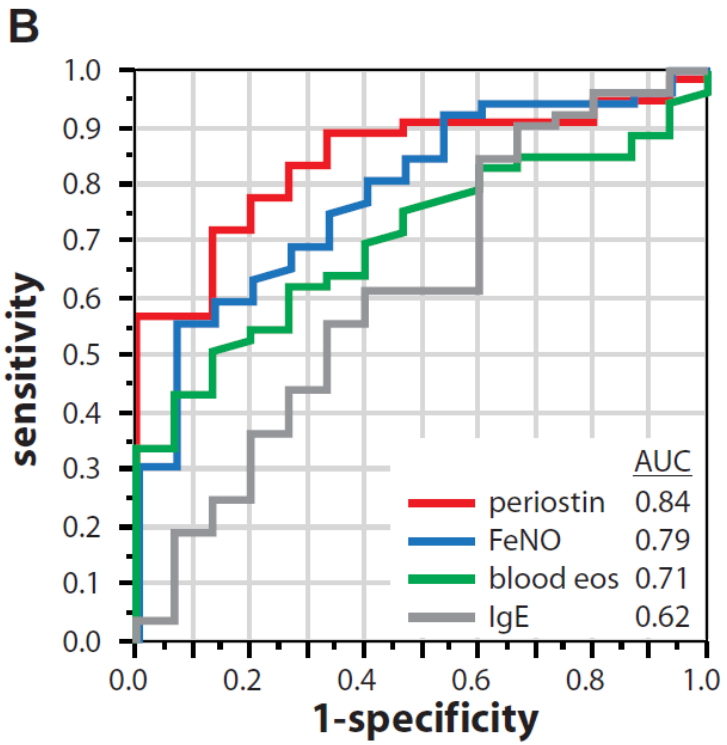


TABLE II. Logistic regression model of biomarkers versus eosinophil status in BOBCAT (n = 59)

	Estimate	SE	*z* Score	*P* value
Age	−0.0396	0.039	−1.015	.31
Sex (male)	−0.2031	0.889	−0.229	.82
Body mass index	−0.1004	0.066	−1.527	.13
Blood eosinophils	1.7482	3.621	0.483	.63
Serum IgE	−0.0002	0.001	−0.100	.92
FENO	0.0476	0.038	1.238	.22
Serum periostin	0.2491	0.092	2.719	.007

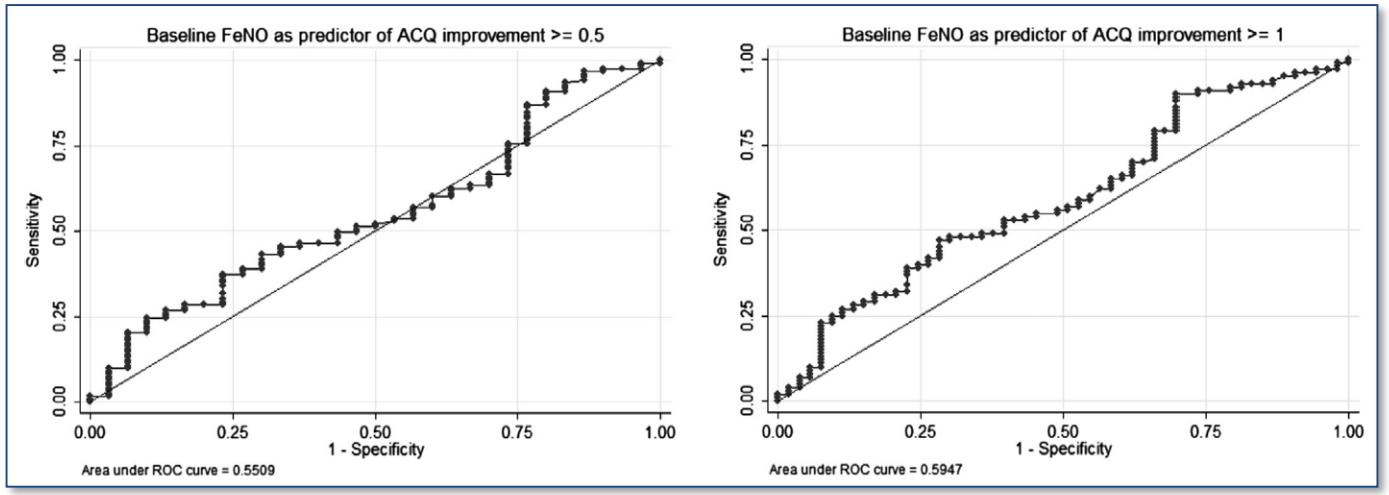
Jia G, et al. J Allergy Clin Immunol 2012;130:647-54

FeNO as a Predictor of ICS response

- 153 patients with asthma

Table 2
Factors associated with achieving asthma improvement and/or control ($n = 146$). Results presented as adjusted odds ratios (aOR) and 95% confidence interval (CI) from multiple logistic regression analyses where all variables listed in the first column were predictors and achieving asthma improvement and/or control was outcome. An association is significant if the CI does not include 1.

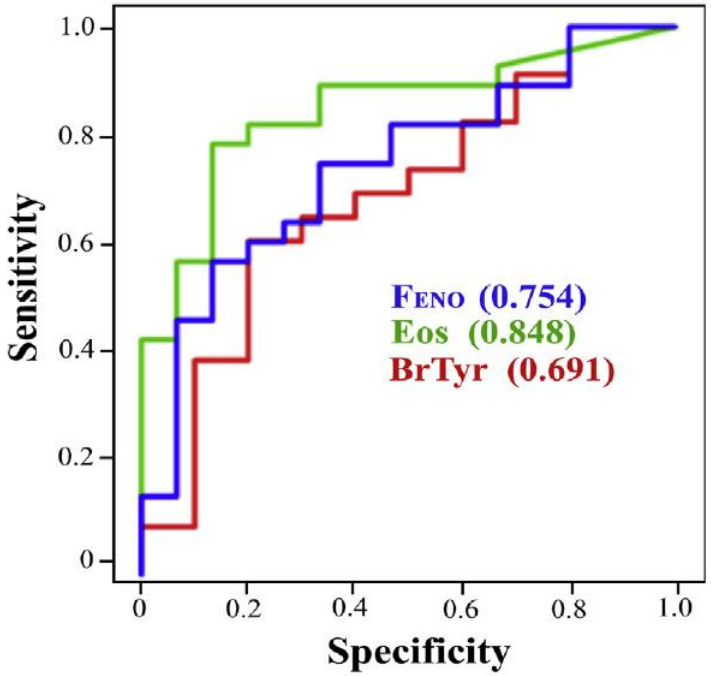
	Achieving improvement of ACQ with 0.5 ($n = 123$)	Achieving improvement of ACQ with 1 ($n = 100$)	Achieving improvement of ACQ with 1 and asthma control (ACQ $\leqslant$ 0.75) ($n = 45$)
Displaying intermediate FeNO vs low FeNO	1.53 (0.33, 7.12)	7.63 (1.65, 35.3)	9.46 (1.11, 80.8)
Displaying high FeNO vs low FeNO	1.23 (0.33, 4.63)	4.10 (1.10, 15.2)	14.0 (1.75, 112)
ACQ at initial visit (per ACQ unit)	3.27 (1.86, 5.76)	5.81 (3.17, 10.7)	1.32 (0.92, 1.88)
Height (per 10 cm)	1.06 (0.47, 2.40)	1.40 (0.65, 3.03)	1.28 (0.67, 2.42)
Age (per 10 years)	1.22 (0.84, 1.77)	1.07 (0.74, 1.55)	1.03 (0.77, 1.37)
FEV_1 (per 10% pred)	1.20 (0.84, 1.70)	1.20 (0.88, 1.65)	1.20 (0.94, 1.54)
Female gender	1.02 (0.23, 4.61)	1.41 (0.34, 5.84)	1.87 (0.59, 5.93)
Atopy	1.31 (0.23, 7.35)	0.34 (0.06, 1.97)	0.73 (0.22, 2.41)
Time to follow-up (per 10 days)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)
Dose of ICS (per 100 microgram)	1.05 (0.85, 1.30)	0.91 (0.77, 1.08)	0.96 (0.85, 1.10)

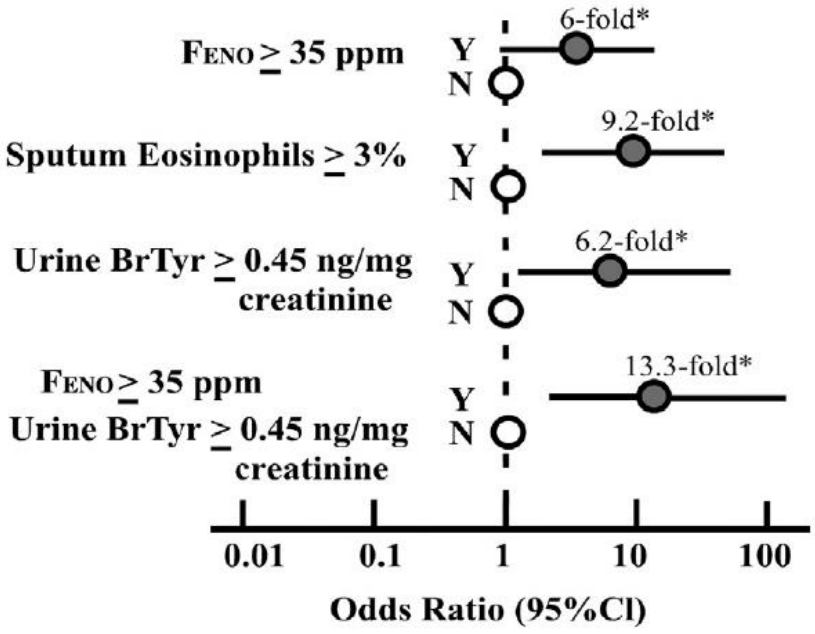


Malinovschi A, et al. Nitric Oxide 2014;40:110-6

Response to ICS

- 46 patients with stable persistent asthma





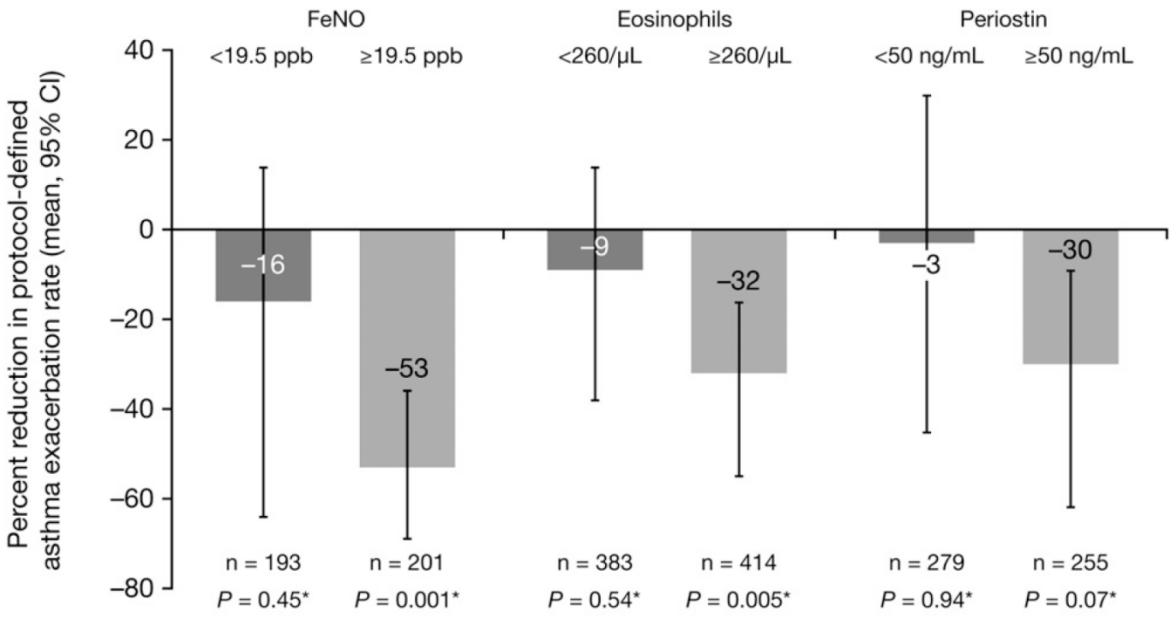
Cowan DC, et al. J Allergy Clin Immunol 2015;135:877-83

Anti-IgE (Omalizumab)

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study

- 850 patients with uncontrolled severe persistent allergic asthma

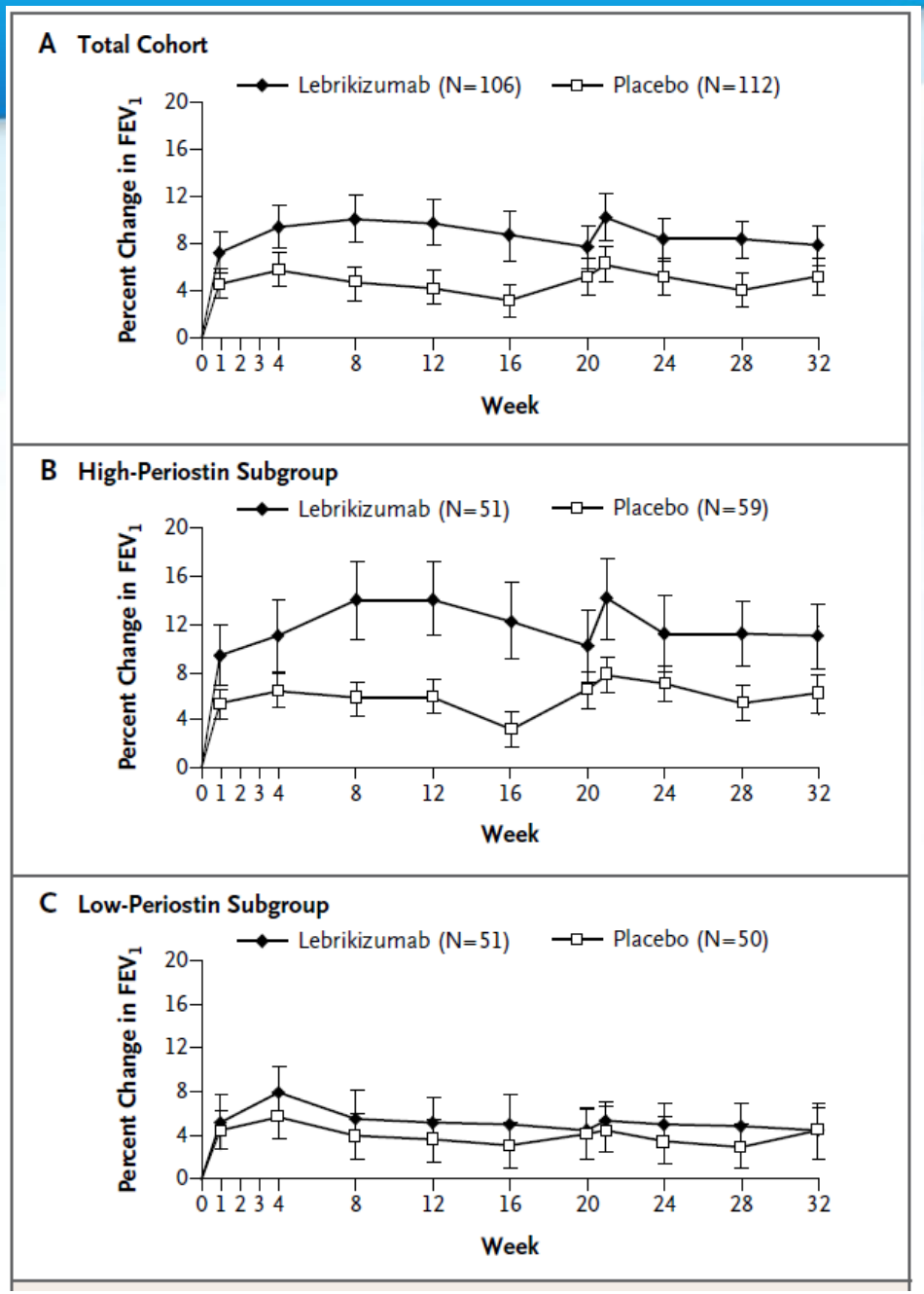


Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania N, et al. Am J Respir Crit Care Med 2013;187:804-11

Anti-IL-13 (Lebrikizumab)

- 219 adults with asthma that was inadequately controlled despite ICS therapy
- Patients with high pretreatment levels of serum periostin had greater improvement in lung function with lebrikizumab than did patients with low periostin levels.

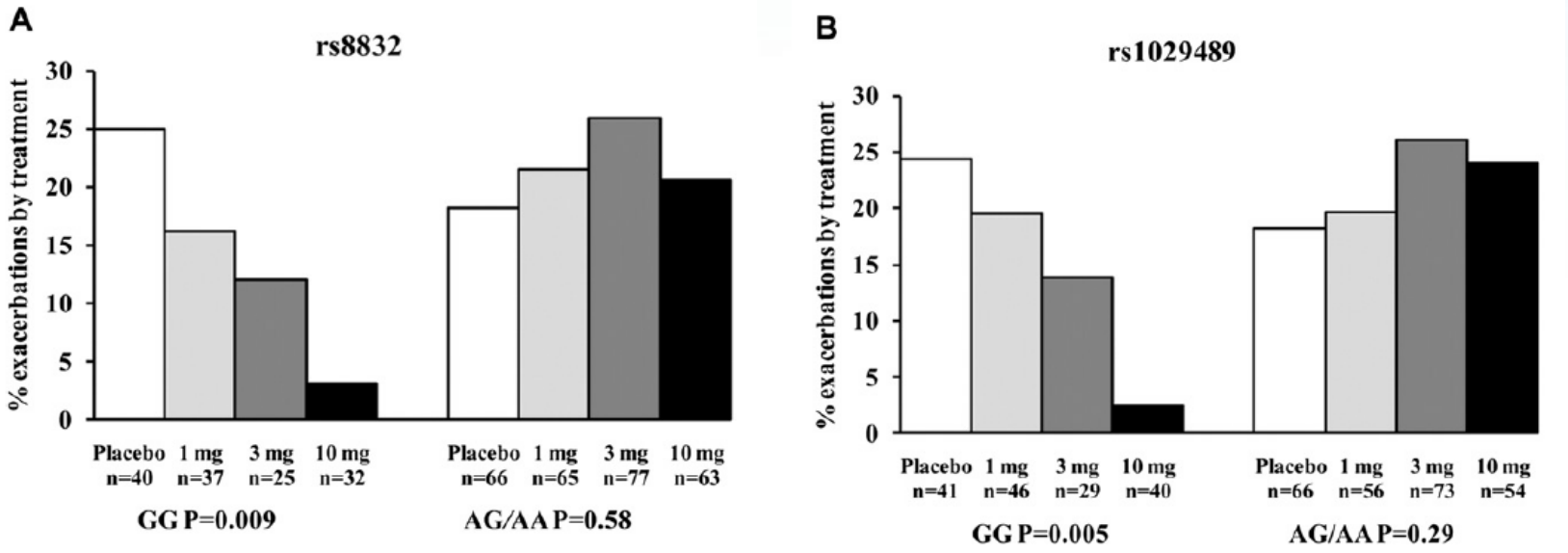


Corren J , et al. N Engl J med 2011;365:1088-98

Inhaled IL-4Rα antagonist (Pitrakinra)

IL-4 receptor polymorphisms predict reduction in asthma exacerbations during response to an anti–IL-4 receptor α antagonist

- Nineteen IL-4 receptor α gene (IL4RA) SNP were tested in 407 subjects



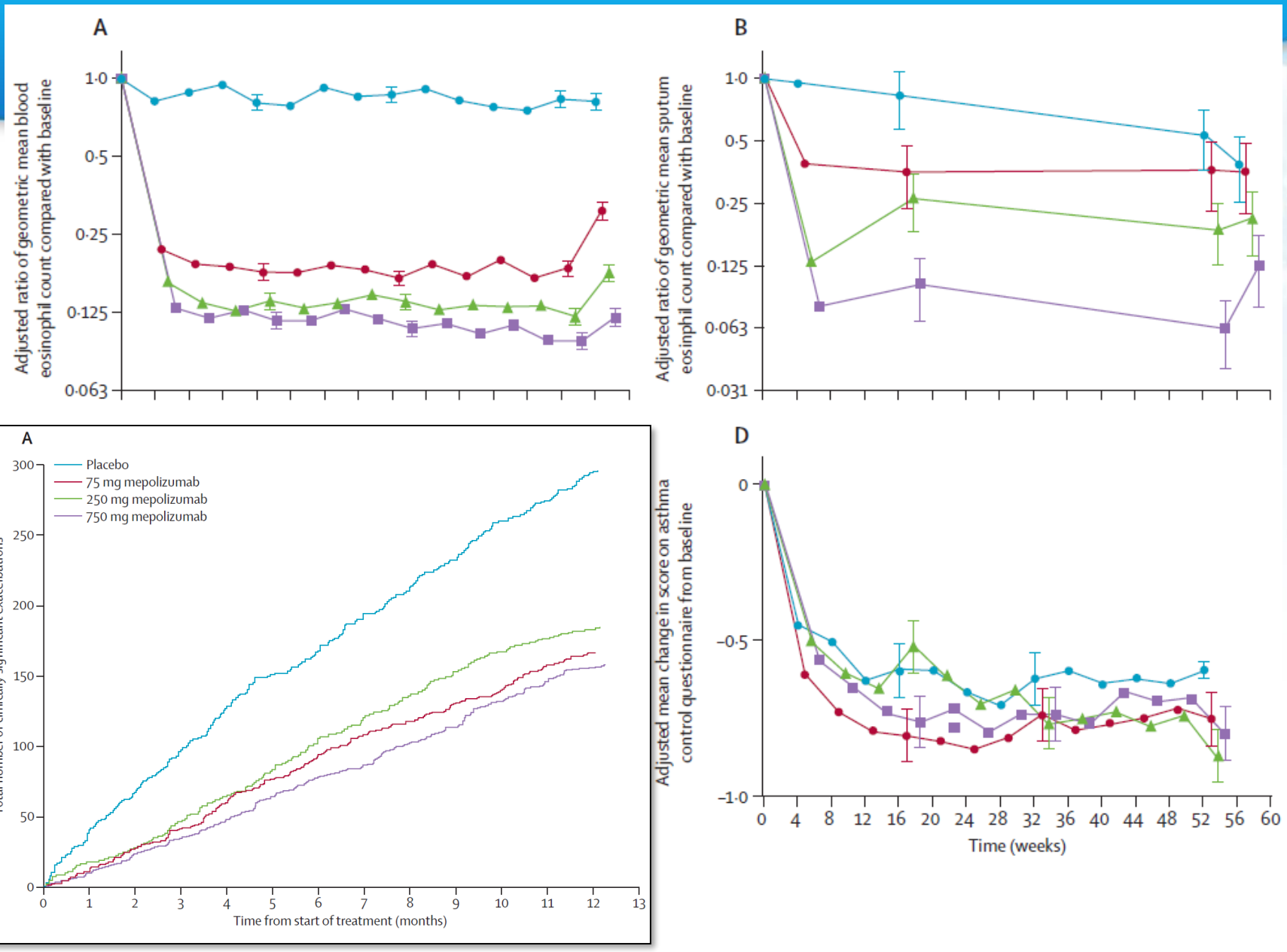
Slager RE, et al. J Allergy Clin Immunol 2012;130:516-22

Anti-IL-5 (Mepolizumab)

- Mepolizumab for severe eosinophilic asthma (DREAM)
  - A multicenter, double-blind, placebo-controlled trial
  - 621 patients (81 centers in 13 countries including Korea)

- a history of two or more exacerbations requiring systemic corticosteroid
- evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year:
  a sputum eosinophil count of 3% or more,
  an FeNO of 50 ppb or more,
  an peripheral blood eosinophil count of 0.3×10^9 per L or more

Pavord ID, et al. Lancet 2012;380:651-9



Pavord ID, et al. Lancet 2012;380:651-9

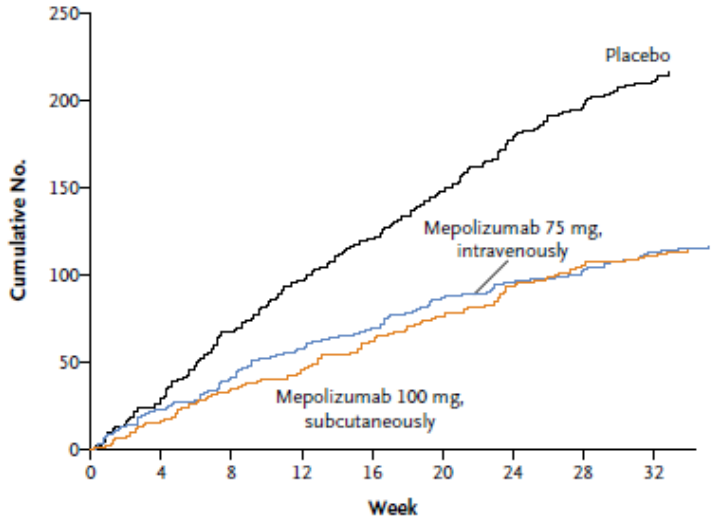
Anti-IL-5 (Mepolizumab)

- MEpolizumab as Adjunctive Therapy IN Patients with Severe Asthma (MENSA)
  - A multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled trial
  - 576 patients (119 centers in 16 countries including Korea)

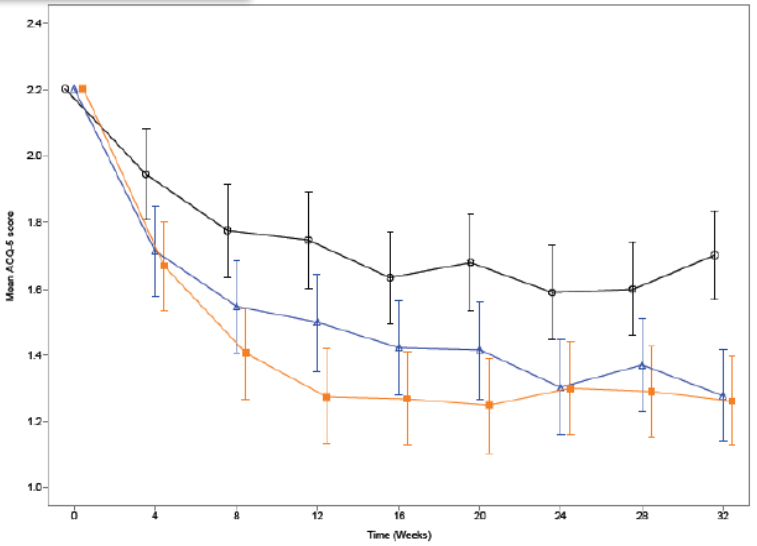
- at least two exacerbations in the previous year that were treated with systemic glucocorticoids (despite high doses of ICS)
- Blood eosinophil count of at least 150 cells per microliter at screening or at least 300 cells per microliter at some time during the previous year

Ortega HG, et al. N Engl J med 2014;371:1198-207

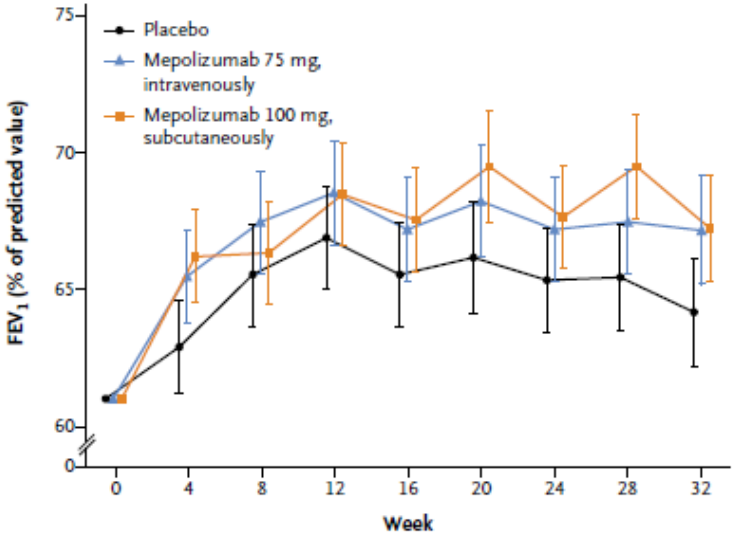
Exacerbation



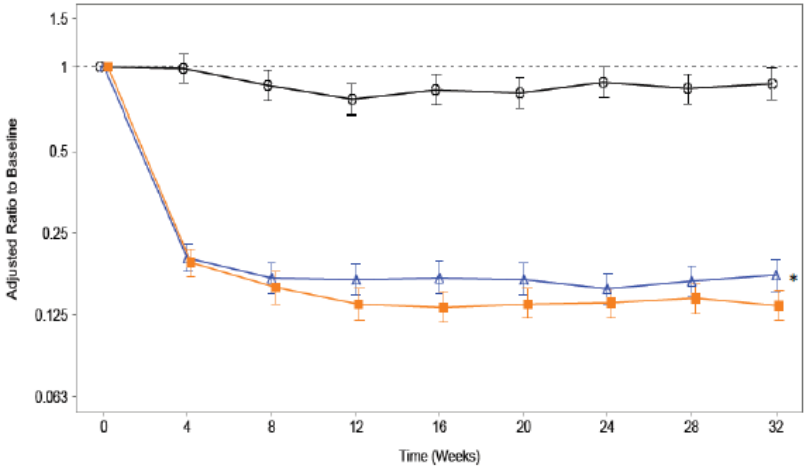
ACQ-5



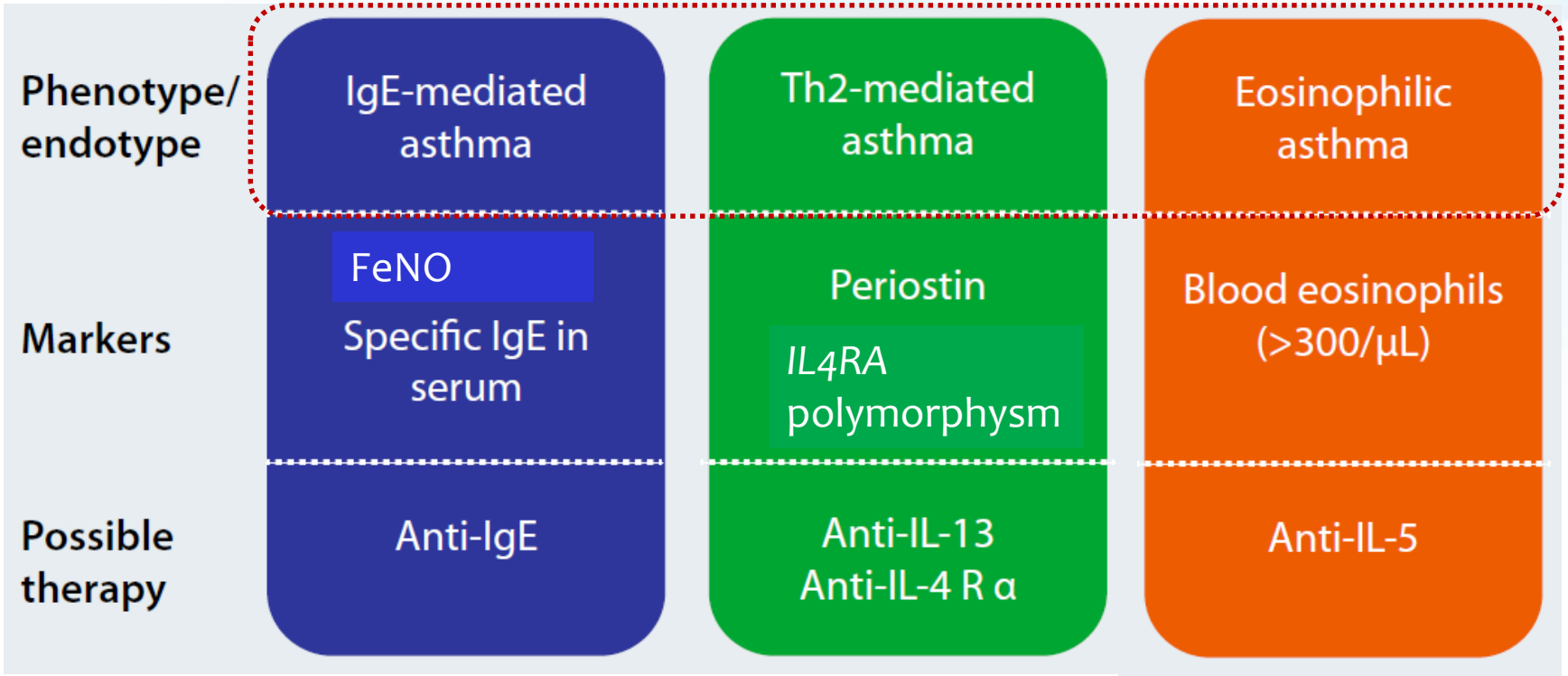
FEV_1



Blood Eosinophil



Phenotypes and Possible Specific Treatments



Macrolide for Asthma

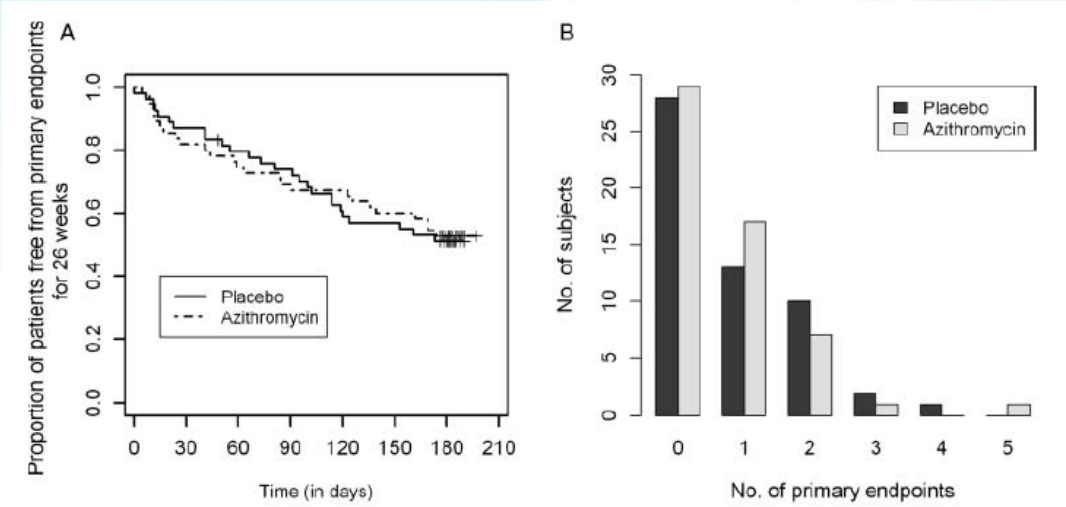
Comparison 1. Macrolide versus placebo

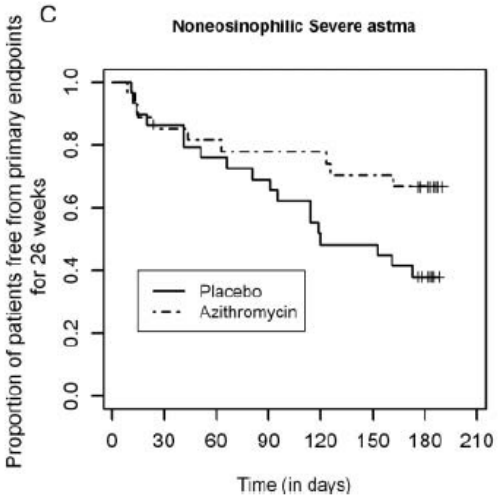
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation requiring hospitalisation	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.13, 7.23]
2 'Severe' exacerbation - requiring at least OCS	5	290	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.43, 1.57]
3 Symptom scales	4	156	Std. Mean Difference (Fixed, 95% CI)	-0.04 [-0.36, 0.28]
4 Asthma Control	4	353	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.26, 0.15]
5 Asthma Quality of Life Questionnaire (AQLQ)	5	389	Mean Difference (Fixed, 95% CI)	0.06 [-0.12, 0.24]
6 Rescue medication puffs/day	4	314	Mean Difference (Fixed, 95% CI)	-0.26 [-0.65, 0.12]
7 Morning PEF (L/min)	4	289	Mean Difference (Fixed, 95% CI)	2.22 [-9.73, 14.17]
8 Evening PEF (L/min)	3	212	Mean Difference (Fixed, 95% CI)	1.97 [-12.68, 16.62]
9 FEV_1 (L)	9	631	Mean Difference (Fixed, 95% CI)	0.08 [0.02, 0.14]
10 Bronchial hyperresponsiveness (BHR)			Other data	No numeric data
11 Oral corticosteroid dose	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Serious adverse events (incl mortality)	7	434	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.24, 2.68]
13 Withdrawal	9	563	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.52]
14 Blood eosinophils	2		Mean Difference (Fixed, 95% CI)	-33.50 [-36.11, -30.90]
15 Sputum eosinophils	3		Mean Difference (Fixed, 95% CI)	Totals not selected
16 ECP in serum	2		Mean Difference (Fixed, 95% CI)	-12.84 [-15.67, -10.00]
17 ECP in sputum	2		Mean Difference (Fixed, 95% CI)	-1.45 [-1.78, -1.11]

Kew KM ,et al. Cochrane Database Syst Rev 2015

Azithromycin in Non-eosinophilic Asthma

- 109 subjects with exacerbation-prone severe asthma
- 250 mg azithromycin for 5days and then 3 times a week
- 26week treatment
- Non-eosinophilic asthma
  : FeNO <upper limit of normal and blood Eo ≤ 200/μl





Brusselle GG, et al. Thorax 2013;68:322-9

SUMMARY

- Stratification of asthma phenotypes (observable characteristics) and endotypes (biologic mechanism) with appropriate use of biomarkers may lead to personalized treatment.
- Th2-associated asthma tends to be responsive to corticosteroids.

Phenotype	Responsive to therapy
Early-onset allergic	Corticosteroid, Anti-IgE, Anti-IL-13, Anti-IL-4Rα
Late-onset eosinophilic	Anti-IL-5, LT modifiers
Exercise-induced	LT modifiers, anti-IL-9
Obesity-related	Weight loss
Neutrophilic	Macrolide antibiotics

- Biomarkers as predictors of ICS

  : blood eosinophils, FeNO, periostin

Thank You for Your Attention