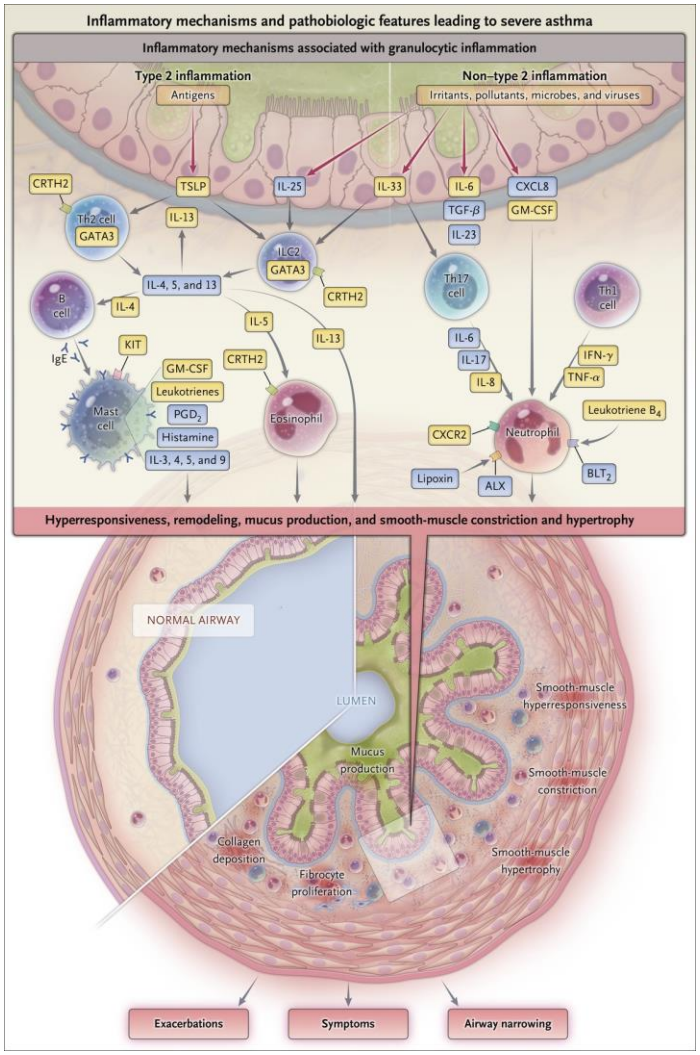
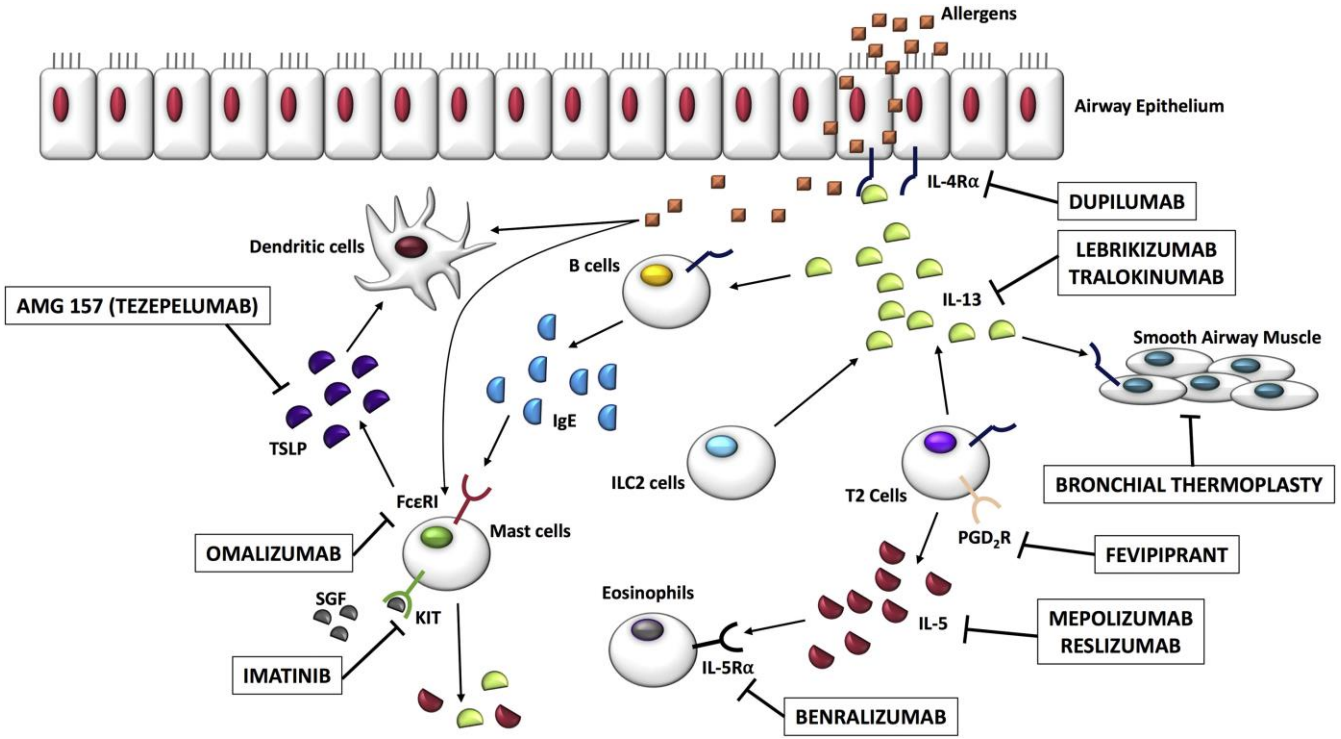
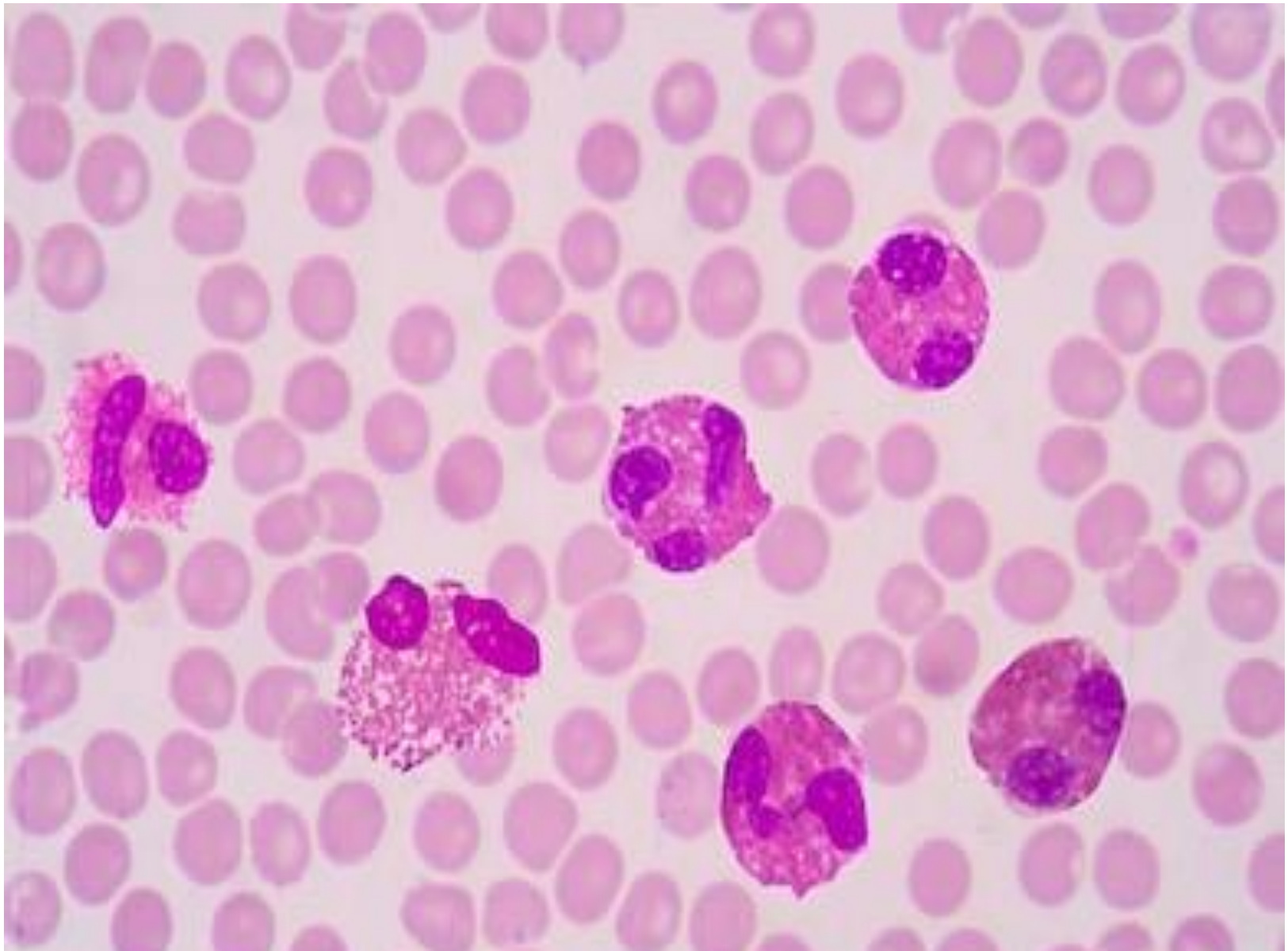
Eosinophilic Asthma and Role of New Biologics

Stuart A Friedman MD
Allergy-Immunology
Boca Raton Regional Hospital

Xolair 2003	omalizumab	Anti IgE	Moderate to severe asthma with positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ics, 6+
Nucala 2015	mepolizumab	Interleukin -5 antagonist	Add on maintenance Severe asthma, 12+ eosinophilic phenotype & (EGPA) eosinophilic granulomatosis with polyangiitis (adults)
Cinqair 2016	reslizumab	Interleukin-5 antagonist	Add-on maintenance Severe asthma, 18+, eosinophilic phenotype
Fasenra 2017	benralizumab	IL-5 receptor cytolytic	Add-on maintenance, severe asthma, 12+ eosinophilic phenotype
Dupixent 2018	dupilumab	IL-4 receptor antagonist	Add-on, moderate to severe asthma, eosinophilic phenotype or with oral corticosteroid dependent asthma

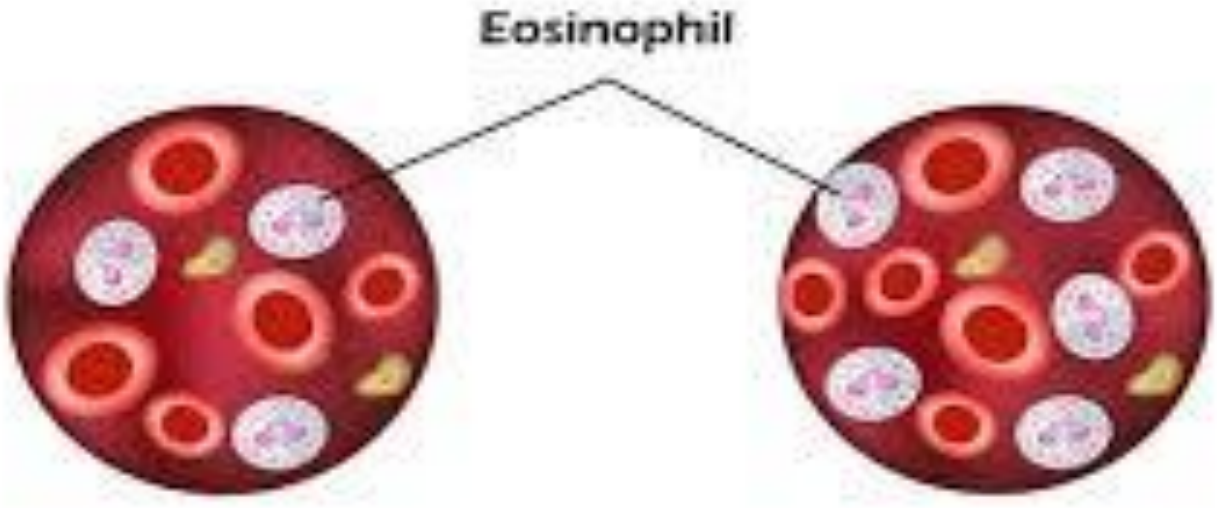






Eosinophilia

(eosinophils above normal range in blood)



Normal

Eosinophils normal range

Eosinophilia

Easinophils above normal range

WAO's mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

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Volume 6, Issue 6

WAO Events and Programs - June 2009

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A man with swollen eyes
Written by Manli Qing, MD and Bob Lanier, MD

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Phillip A. Lieberman, MD
Clinical Professor of Medicine and Pediatrics
University of Tennessee College of Medicine

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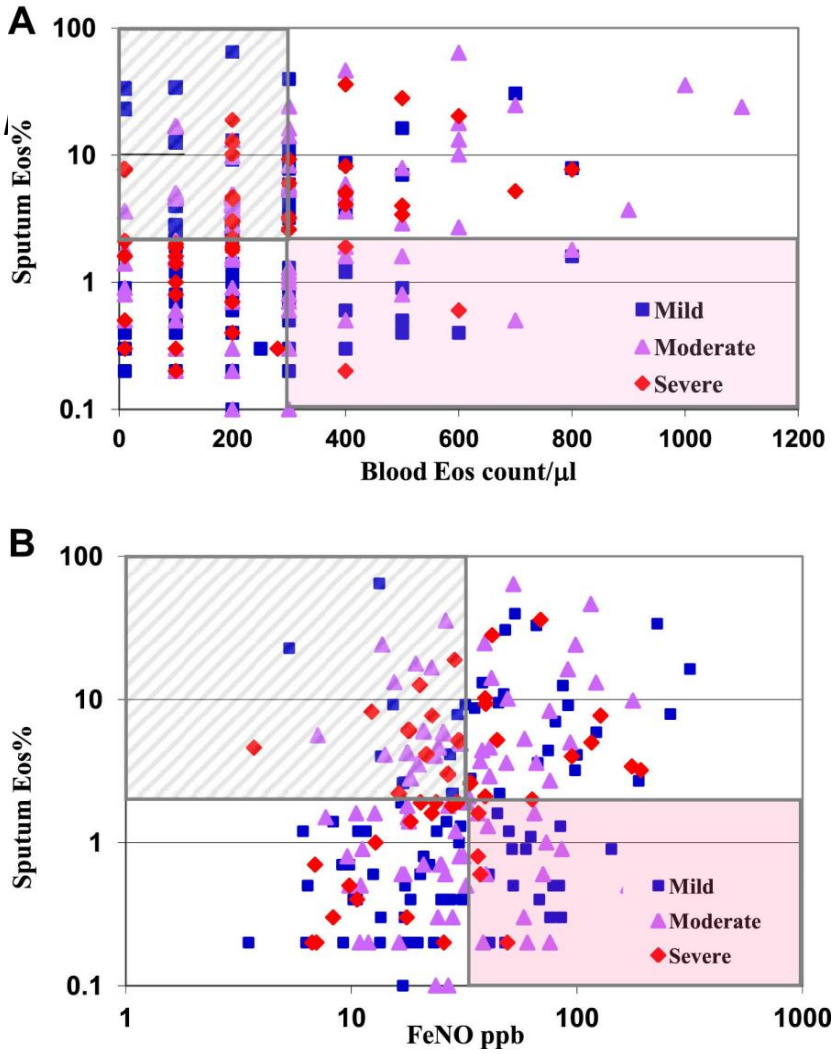
Pensacola Allergy Society
July 16, 2009

Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects

Annette T. Hastie, PhD, Wendy C. Moore, MD, Huashi Li, MS, Brian M. Rector, MS, Victor E. Ortega, MD, Rodolfo M. Pascual, MD, Stephen P. Peters, MD, PhD, Deborah A. Meyers, PhD, Eugene R. Bleecker, MD

Journal of Allergy and Clinical Immunology
Volume 132, Issue 1, Pages 72-80.e12 (July 2013)
DOI: 10.1016/j.jaci.2013.03.044

What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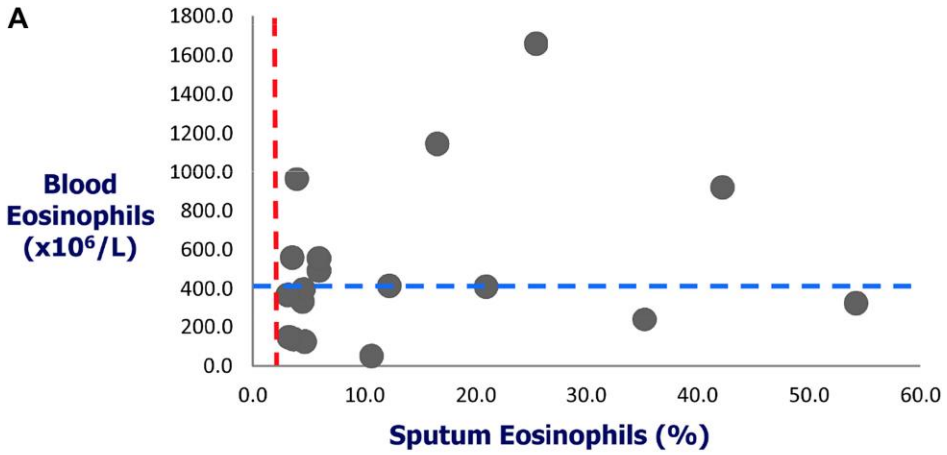
Mild
Moderate
Severe

What is an "eosinophilic phenotype" of asthma?

Parameswaran Nair, MD, PhD, FRCP, FRCPC

Journal of Allergy and Clinical Immunology
Volume 132, Issue 1, Pages 81-83 (July 2013)
DOI: 10.1016/j.jaci.2013.05.007

A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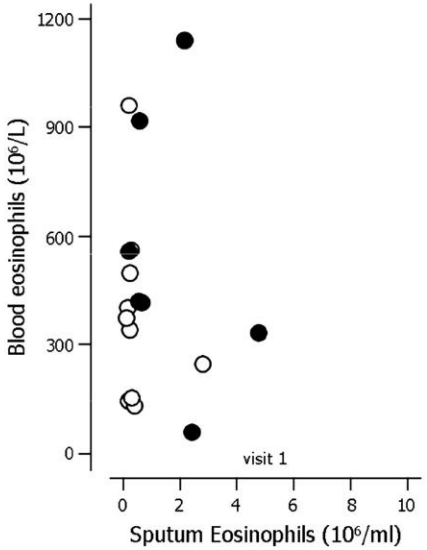
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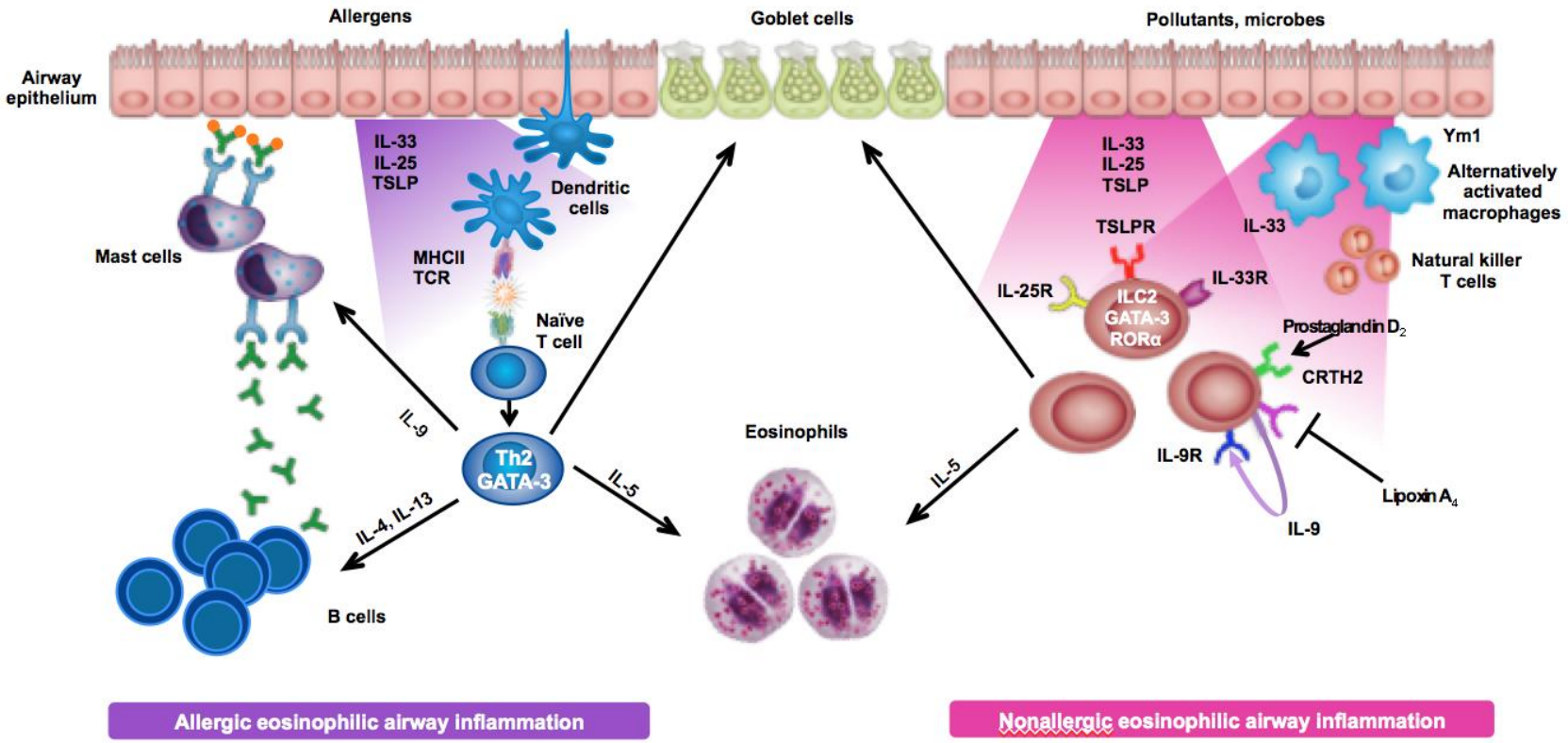
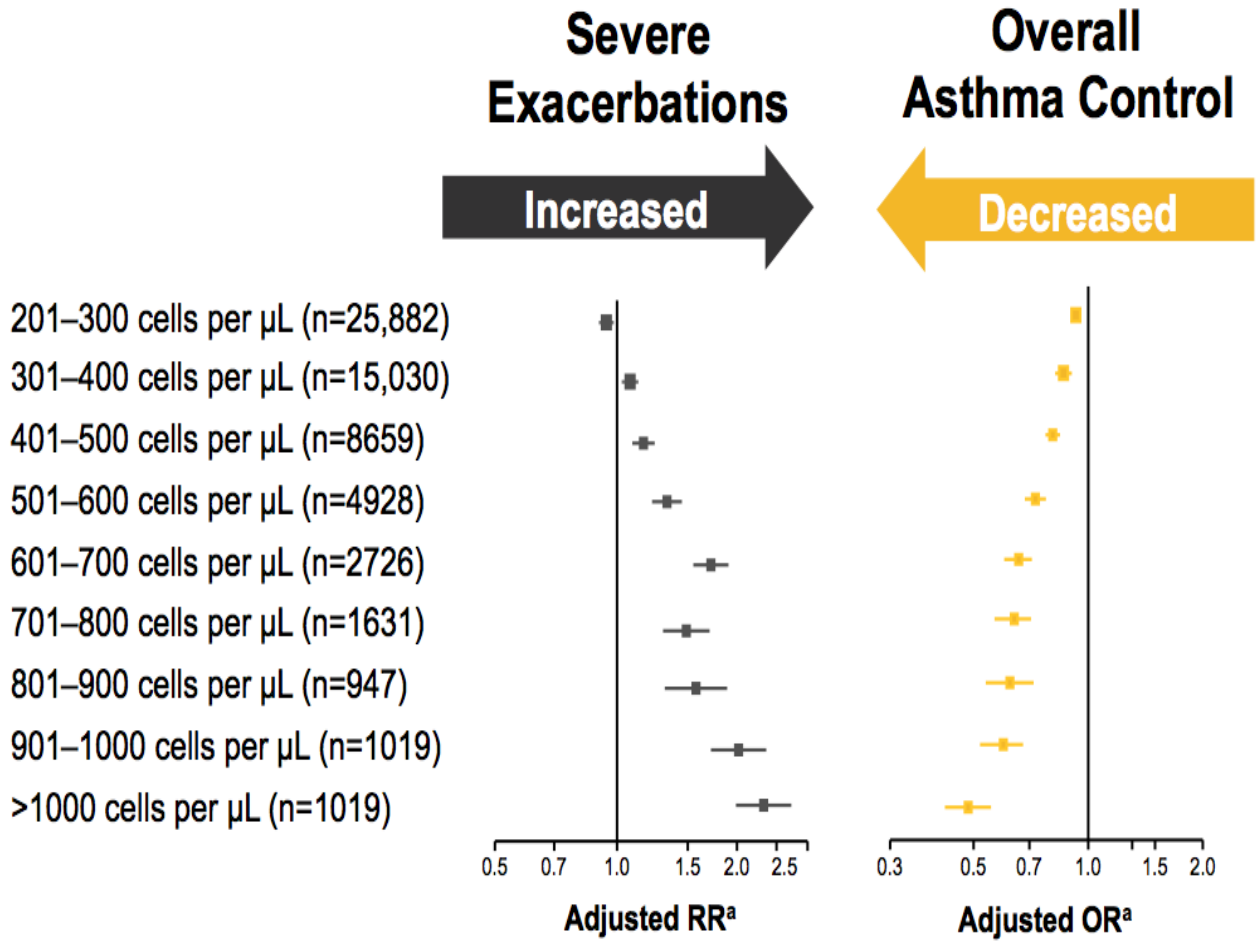
Eosinophils Can Be a Component of Both Allergic and Nonallergic Asthma



IL=interleukin; ILC=innate lymphoid cell; MHC=major histocompatibility complex; TCR=T cell antigen receptor; TSLP(R)=thymic stromal lymphopoietin (receptor).
Adapted from Lambrecht BN, Hammad H. *Nat Immunol.* 2015;16:45-56.

Elevated Peripheral Blood Eosinophils Are Associated With Poor Asthma Control and Exacerbations



In a sub-population analysis of 54,072 patients, a peripheral blood eosinophil level above 300 cells/µL (n=16,602) was associated with a 30% increased rate of severe exacerbations

[a]Data from medical records of asthmatics aged 12–80 years with 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients assigned to 9 eosinophil count categories compared with a reference category of 200 cells per µL or less (N=68,407). Adjusted for age, sex, body-mass index, smoking status, and Charlson comorbidity index score.
OR=odds ratio; RR=rate ratio.
Adapted from Price DB, et al. *Lancet Respir Med.* 2015;3(11):849-858.

Elevated Peripheral Blood Eosinophil Levels Correlate With Several Asthma Outcomes

Asthma outcomes with unadjusted rate ratio or risk ratio in 2011 by blood eosinophil cutoff point of 400/mm^3 in 2010

Asthma outcomes in 2011	Eosinophil ≥400/mm^3, no. (%) (n=437)	Eosinophil <400/mm^3, no. (%) (n=1955)	Unadjusted rate ratio or risk ratio (95% CI)[a]	*P* value[a]
Asthma exacerbation	0.57[b]	0.37[b]	1.52 (1.23–1.88)	<0.001
Any asthma exacerbation	142 (32.5)	465 (23.8)	1.37 (1.17–1.60)	<0.001
≥2 Asthma exacerbations	50 (11.4)	154 (7.9)	1.45 (1.07–1.96)	0.02
Any asthma ED visit	46 (10.5)	116 (5.9)	1.77 (1.28–2.46)	<0.001
Any asthma hospitalization	19 (4.3)	38 (1.9)	2.24 (1.30–3.84)	0.004
Any asthma ED and/or hospitalization	46 (10.5)	120 (6.1)	1.71 (1.24–2.37)	0.001
≥7 SABA canisters dispensed	150 (34.3)	475 (24.3)	1.41 (1.21–1.64)	<0.001

ED=emergency department; SABA=short-acting β_2-agonist.

[a]Negative binomial and Poisson regression models with robust error variance were used to estimate the rate ratio and risk ratio, respectively, their 95% CIs, and to derive the *P* values.

[b]Data are rate/y.

Zeiger RS, et al. *J Allergy Clin Immunol Pract*. 2014;2(6):741-750.

Interleukin-5 (IL-5) Is One of Several Cytokines Regulating Eosinophil Function[1-3]

IL-4	IL-5	IL-13
IL-25	IL-33	INF-γ
Eotaxin	GM-CSF	TSLP

IL-5 is produced by many cell types and regulates eosinophil biology by binding the IL-5 receptor, which is highly expressed on the eosinophil cell surface[3]

Multiple Cell Types Contribute to Asthma

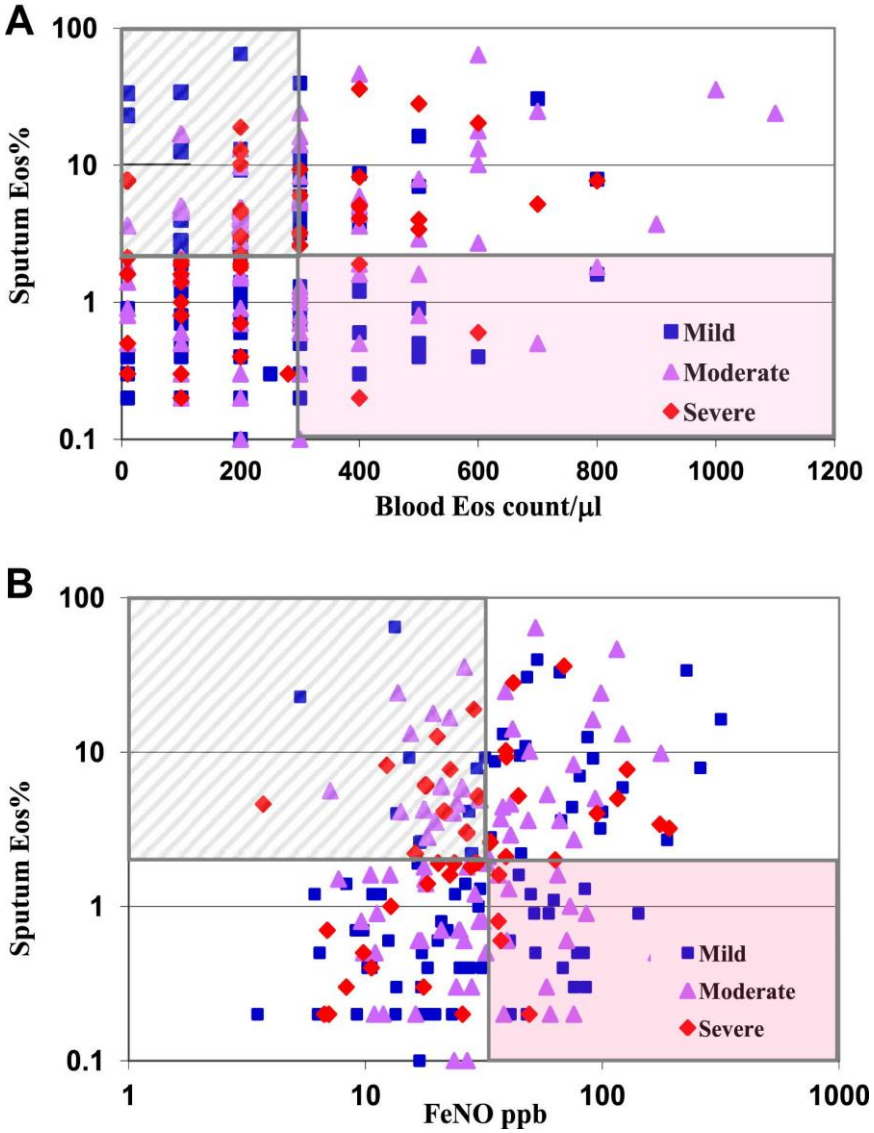
Inflammatory Cells[1]

- Eosinophils
- Dendritic cells
- ILC2 cells
- Macrophages
- Mast cells
- Neutrophils
- T lymphocytes

Structural Cells[1]

- Airway epithelial cells
- Airway smooth muscle cells
- Endothelial cells
- Fibroblasts
- Goblet cells
- Myofibroblasts
- Airway nerves

Eosinophils are a major contributor to severe asthma because they can lead to progressive airway damage.[2,3] Increased airway eosinophils occur in approximately 50% of severe asthma patients[4]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Moderate
Severe

Global Initiative for Asthma (GINA)

What's new in GINA 2018?

GINA Global Strategy for Asthma Management and Prevention

GINA Definition of Severe Asthma

In Children ≥6 Years of Age, Adolescents, and Adults

Asthma Severity Is Assessed Retrospectively Based Upon the Level of Treatment Required to Control Symptoms and Exacerbations

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred Controller Choice		Low-dose ICS	Low-dose ICS/LABA[a]	Severe Asthma Med-/high-dose ICS/LABA	Refer for add-on treatment
	Other Controller Options				
Reliever	As-needed SABA		As-needed SABA or low-dose ICS/LABA[b]		

[a]For children 6-11 years, the preferred Step 3 treatment is medium-dose ICS.

[b]For patients prescribed certain ICS/LABA maintenance and reliever therapies.

Identifying Severe Asthma: GINA and ERS/ATS Definitions of Severe Asthma

GINA[1]

(In children ≥6 years of age, adolescents, and adults)

- Severe asthma is asthma that requires Step 4 or Step 5 treatment with medium- or high-dose ICS/LABA (+/- additional controllers) in order to prevent asthma from becoming uncontrolled
- Asthma that remains uncontrolled despite Step 4 or Step 5 treatment

ERS/ATS Guidelines[2]

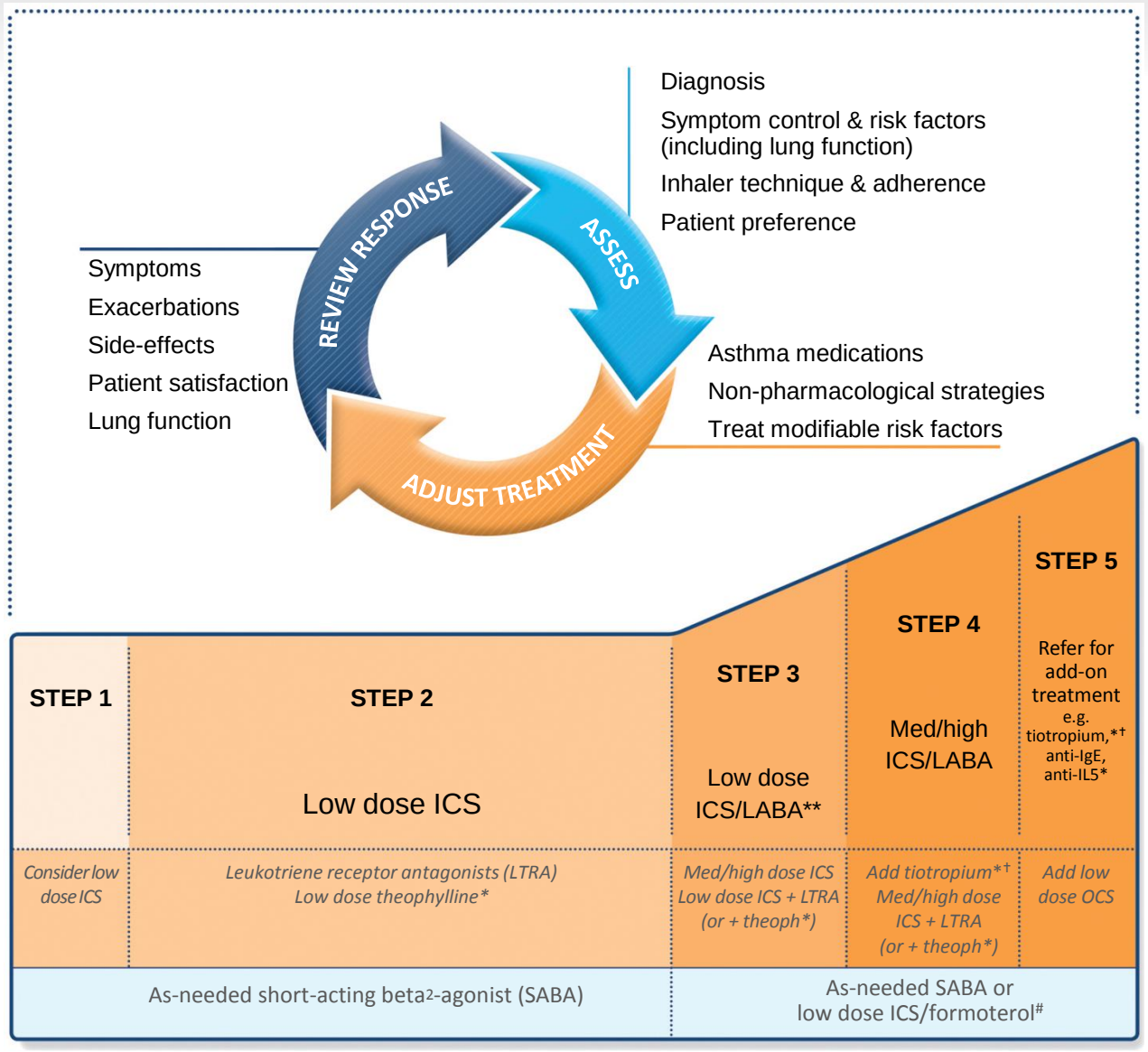
(In youths ≥6 years of age and adults)

- Severe asthma is asthma that requires treatment with GINA Step 4 or Step 5 therapy for the previous year
- Or asthma that requires systemic corticosteroids ≥50% of the previous year in order to maintain control or asthma that remains uncontrolled despite therapy

ATS=American Thoracic Society; ERS=European Respiratory Society; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroids; LABA=long-acting beta$_2$ agonist.

1. Adapted from GINA. Global Strategy for Asthma Management and Prevention. 2018. http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed April 9, 2018. 2. Chung KF, et al. *Eur Respir J.* 2014;43(2):343-373.

Stepwise management - pharmacotherapy



*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

ERS/ATS Definition of Severe Asthma

In Youths ≥6 Years of Age and Adults

Severe Asthma

- Asthma that requires treatment with GINA Guidelines Steps 4 or 5 therapy for the previous year

Or

- Systemic corticosteroids ≥50% of the previous year to maintain asthma control or asthma that remains uncontrolled despite therapy

Uncontrolled Asthma

(defined by at least one of the following)

- Poor symptom control
- Frequent severe exacerbations
- Serious exacerbations
- Airflow limitation
- Controlled asthma that worsens upon tapering high-dose ICS or systemic corticosteroids

ERS Task Force: Proposed Scheme for Identifying Severe Eosinophilic Asthma in Clinical Practice

Major Criteria[1]

- A diagnosis of severe asthma
- Persistent blood or sputum eosinophilia detected on ≥2 measurements (eg, peripheral blood ≥300 cells/μL)
- Frequent exacerbations (≥2 per/year)
- Need for intermittent or continuous oral corticosteroids to achieve asthma control

Minor Criteria[1,2]

- Late-onset disease[1]
- Chronic rhinosinusitis often with nasal polyps[1]
- Biomarkers[1]
- Fixed airflow obstruction (FEV_1/FVC <70%)[1,2]
- Air trapping and mucus plugs[1]

<u>Key Point:</u> Asthma patients with elevated peripheral blood eosinophils can present with atopy or may be nonatopic as determined by standard diagnostic tests[2,3]

ERS=European Respiratory Society; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

1. Buhl R, et al. *Eur Respir J.* 2017;49. 2. de Groot JC, et al. *ERJ Open Res.* 2016;2. 3. Miranda C, et al. *J Allergy Clin Immunol.* 2004;113:101-108.

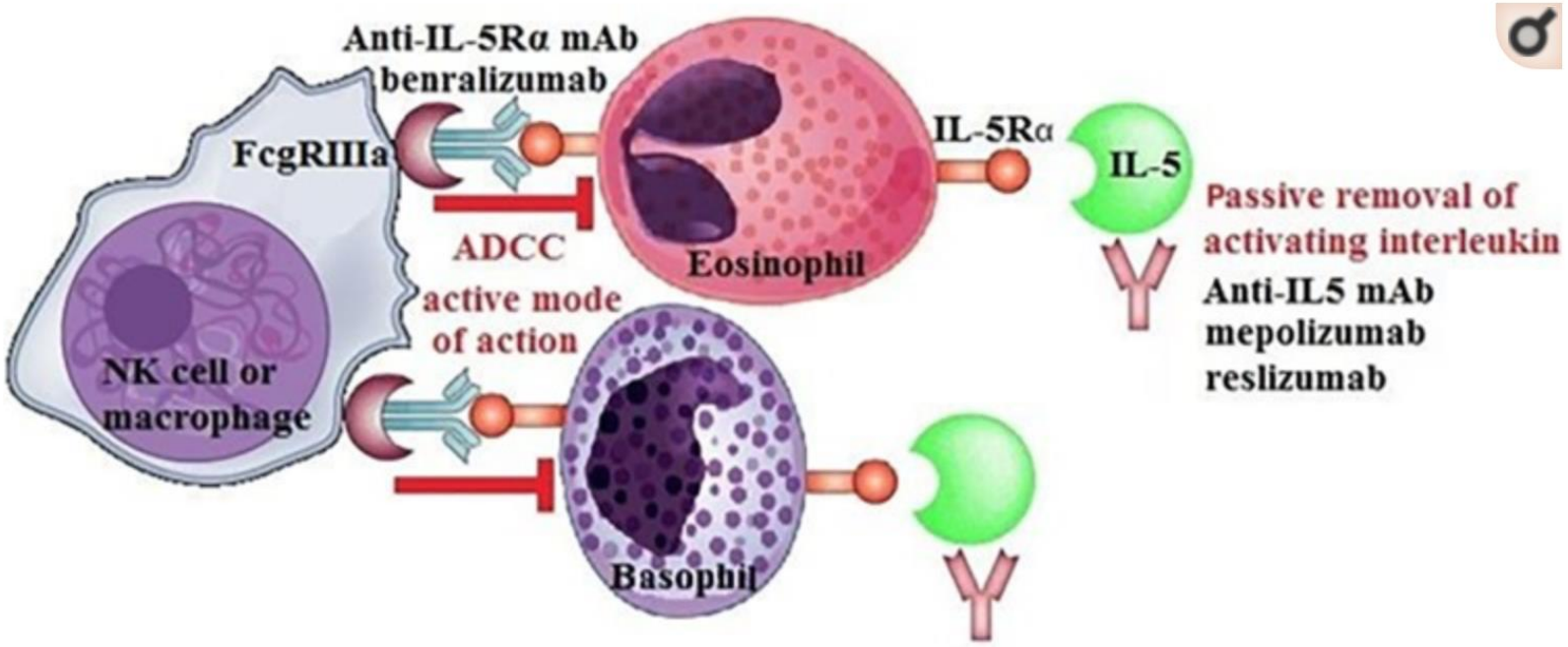
LM 55-year-old male, Fed Ex Driver

History= life-long allergies, more severe since Hurricane Irene, since January 2018, admitted to WBMC twice and Broward Health North once. He estimates that he has over 16 Urgent care/ ER visits during this time period.
Current Medications= Symbicort Incruse, SABA, Allegra and Prednisone. Each time Prednisone weaning takes place he ends up in Urgent Care/ acute care hospital.
Exam= 6'3" and 185 pounds. wheezing.
Cats, Dogs and birds at home
Testing=
Chest X ray= unremarkable
FEV1=36% predicted
Percutaneous Skin Tests= negative to common aeroallergens
Intradermal Skin Testing= deferred
FENO= 66 ppb (normal >25)
Total IgE= 330 kU
CBC= 1.030 absolute eosinophils
ACT= 9

Impression:
Phenotype= eosinophilic asthma (FENO, absolute eosinophil count >1000)
Endotype= allergic asthma adult (IgE)

Plan: benralizumab 30mg monthly x 3 and now every other month
?omalizumab, need to intradermal skin test for a specific allergen and given weight and IgE dosed every other week.
Outcome;
FEV1 has doubled and ACT has doubled as Prednisone has been stopped.

Figure 2



The mechanism of action of therapies targeting IL-5 and its receptor.

Abbreviations: IL, interleukin; ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer; mAB, monoclonal antibody.

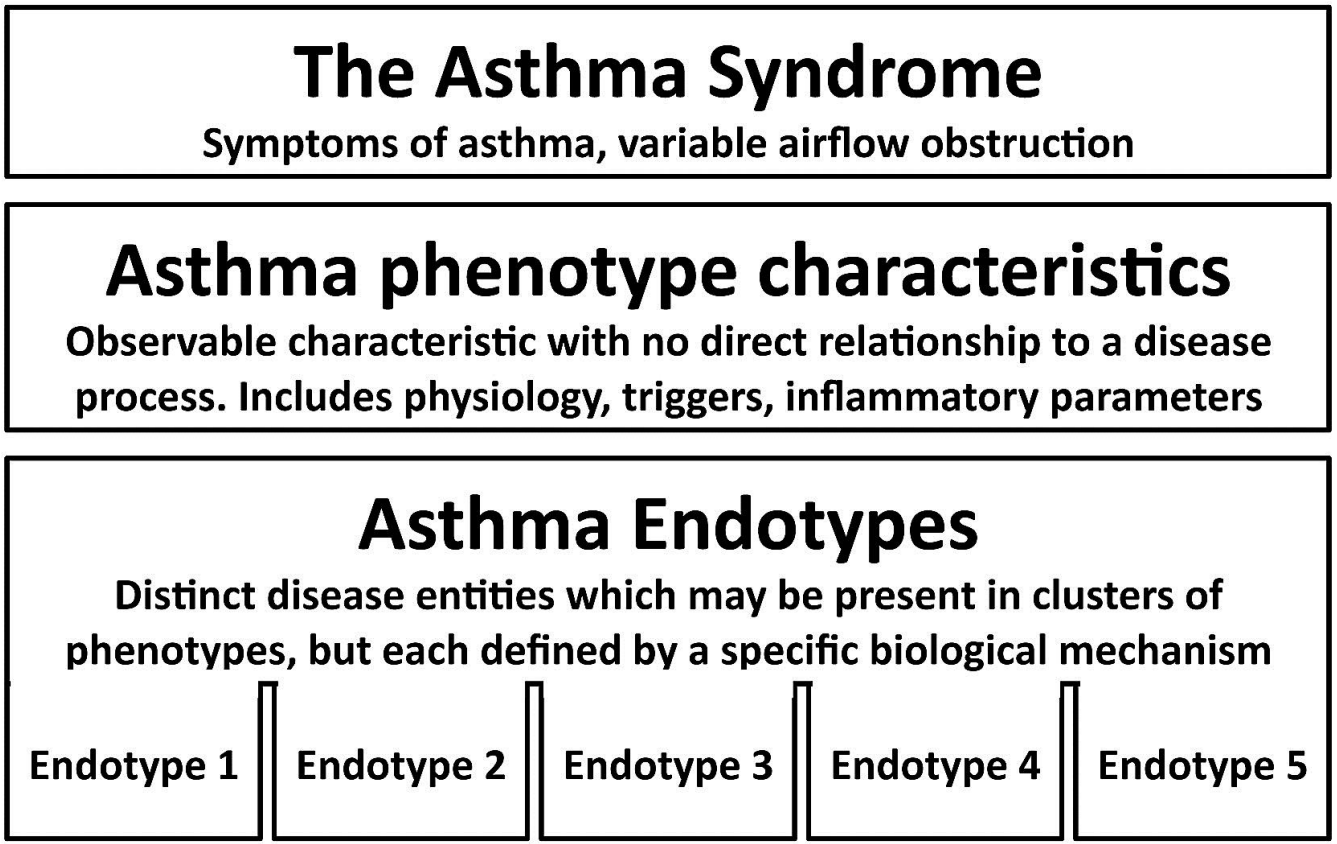


TABLE II. Examples of endotypes that fulfill at least 5 of 7 prespecified disease characteristics

Endotype of the asthma syndrome	Disease characteristics							Proposed mechanism
	Clinical characteristics	Biomarkers	Lung physiology	Genetics	Histopathology	Epidemiology	Treatment response	
Proposed endotype	History, physical examination, comorbidities	Eosinophilia, FeNO, SPT, IgE	BHR, FEV_1, reversibility	SNPs and pathways	Tissue/lung characteristics	Prevalence, risk factors, and natural history	Response or lack of response to a specific treatment	Specific biological pathway or process
Aspirin-sensitive asthma	Polyposis, often more severe asthma	Often eosinophilic, increased urinary LTs	Response to aspirin challenge	LT-related gene polymorphisms	Often eosinophilic	Adult onset, severe disease poor prognosis, prevalence 2% to 5%	Responds to anti-LT, especially 5-LO inhibitors	Likely eicosanoids-related
ABPM	Severe, mucus production, adult/long disease duration	Blood eosinophilia, markedly elevated IgE and specific IgE	Less reversible/fixed airflow obstruction	HLA and rare CF variants	Bronchiectasis/ eosinophils and PMNs, bronchocentric granulomatosis	Long duration/ adult onset/poor prognosis	Glucocorticoids, antifungals, possibly omalizumab	Colonization of airways
Allergic asthma (adults)	Allergen associated symptoms/allergic rhinitis	Positive SPT, elevated IgE/ elevated FeNO	Specific allergic bronchospasm	T_H2 pathway SNPs	Eosinophils, SBM thickening	Childhood onset, history of eczema	Responds to glucocorticoids and omalizumab, possible IL-4/13 pathway inhibition	T_H2–dominant
API-positive preschool wheezer	>3 episodes per year, 1 major or 2 minor characteristics	Often >4% eosinophils in blood (minor), aeroallergen-specific IgE	Potential increased risk of loss of lung function	Unknown	Unknown	Mother or father with asthma	Responds well to daily inhaled glucocorticoids	T_H2–dominant
Severe late-onset hypereosinophilic	Severe exacerbations, late-onset disease	Peripheral blood eosinophilia	Bronchodilator–resistant, episodic fall in lung function, steroid–sensitive	No evidence	High blood eosinophil count and eosinophils in tissue	Approximately 20% of severe asthma populations	Glucocorticoid-sensitive, often oral steroid–dependent, responds to anti–IL-5	Nonatopic, otherwise unknown
Asthma in cross-country skiers	Mild to moderate severity, symptoms mostly related to exercise, URTI commonly reported	FeNO normal, normal blood eosinophil count, increased LTE_4 in urine	Methacholine and or exercise positive, usually negative to mannitol or AMP challenge	Unknown	SBM thickening with low-grade noneosinophilic inflammation, increased neutrophils in sputum related to training intensity or duration, BALT in airway mucosa	15% to 25% of elite skiers, highest prevalence among those training in a cold, dry environment	Responds poorly to inhaled glucocorticoid treatment, improves when training intensity diminishes	Cold, dry air induces chronic stress to the airways, subclinical viral infections?

BALT, Bronchus-associated lymphoid tissue; *BHR,* bronchial hyperresponsiveness; *CF,* cystic fibrosis; *FeNO,* fractional exhaled nitric oxide; *LT,* leukotriene; *LTE_4*, leukotriene E_4; *5-LO,* 5-lipoxygenase; *SBM,* subepithelial basement membrane; *SNP,* single nucleotide polymorphism; *SPT,* skin prick test; *URTI,* upper respiratory tract infection.

Table 1

Clinically Determined and Measured Biomarkers for the Phenotypes and Endotypes of Severe Asthma (adapted from Carr et al[2])

Phenotype	Clinically determined biomarkers and characteristics	Measured biomarkers
Early-onset, allergic asthma	Childhood onset Allergen triggers Allergic rhinitis	Aeroallergen-specific IgE Elevated FeNO Eosinophilia
Early-onset, obesity-exacerbated	Childhood onset Allergen triggers Obesity	Aeroallergen-specific IgE Eosinophilia
Aspirin-exacerbated respiratory disease	Adult onset Nasal polyposis Reactivity to NSAIDs	Eosinophilia Leukotrienes
Allergic bronchopulmonary mycosis	Adult onset Allergy to mold Pronounced mucus production	Markedly elevated total IgE Mold-specific IgE Eosinophilia
Severe late-onset hyper-eosinophilic	Adult onset Severe exacerbations Less atopic Sinusitis Nasal polyps	Eosinophilia
Exacerbation-prone	Frequent exacerbations Sinusitis GERD	Eosinophilia
Neutrophilic	Adult onset Variable severity	Elevated neutrophils in blood and sputum
Obesity-induced, non-eosinophilic	Adult onset Obesity Predominantly female Very symptomatic	Lack of Th2 biomarkers Elevated IL-6 Elevated Leptin
Paucigranulocytic	Mild and severe	Lack of airway inflammation
Asthma with smoking	Current or former tobacco smoke exposure Worse quality of life and more symptoms Corticosteroid insensitivity	Less eosinophilic, more neutrophilic

Abbreviations: IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drugs; GERD, gastroesophageal reflux disease; IL-6, interleukin 6.


NIOX®

Exhaled nitric oxide (FeNO)

- FeNO is becoming more widely available in some countries
- All sections on FeNO have been reviewed and updated
- Decisions about initial asthma treatment
  - GINA recommends at least low dose ICS in almost all patients with asthma, to reduce risk of asthma exacerbations and death
    - SABA-only treatment considered only if symptoms < twice/month, no night waking, and no risk factors for exacerbations
  - In non-smoking patients, FeNO >50 ppb is associated with a good short-term response to ICS in symptoms and lung function
  - There are no studies examining the long-term safety (i.e. for risk of exacerbations) of withholding ICS if initial FeNO is low
  - In patients with a diagnosis or suspected diagnosis of asthma, FeNO can support the decision to start ICS, but cannot safely be recommended for deciding against treatment with ICS

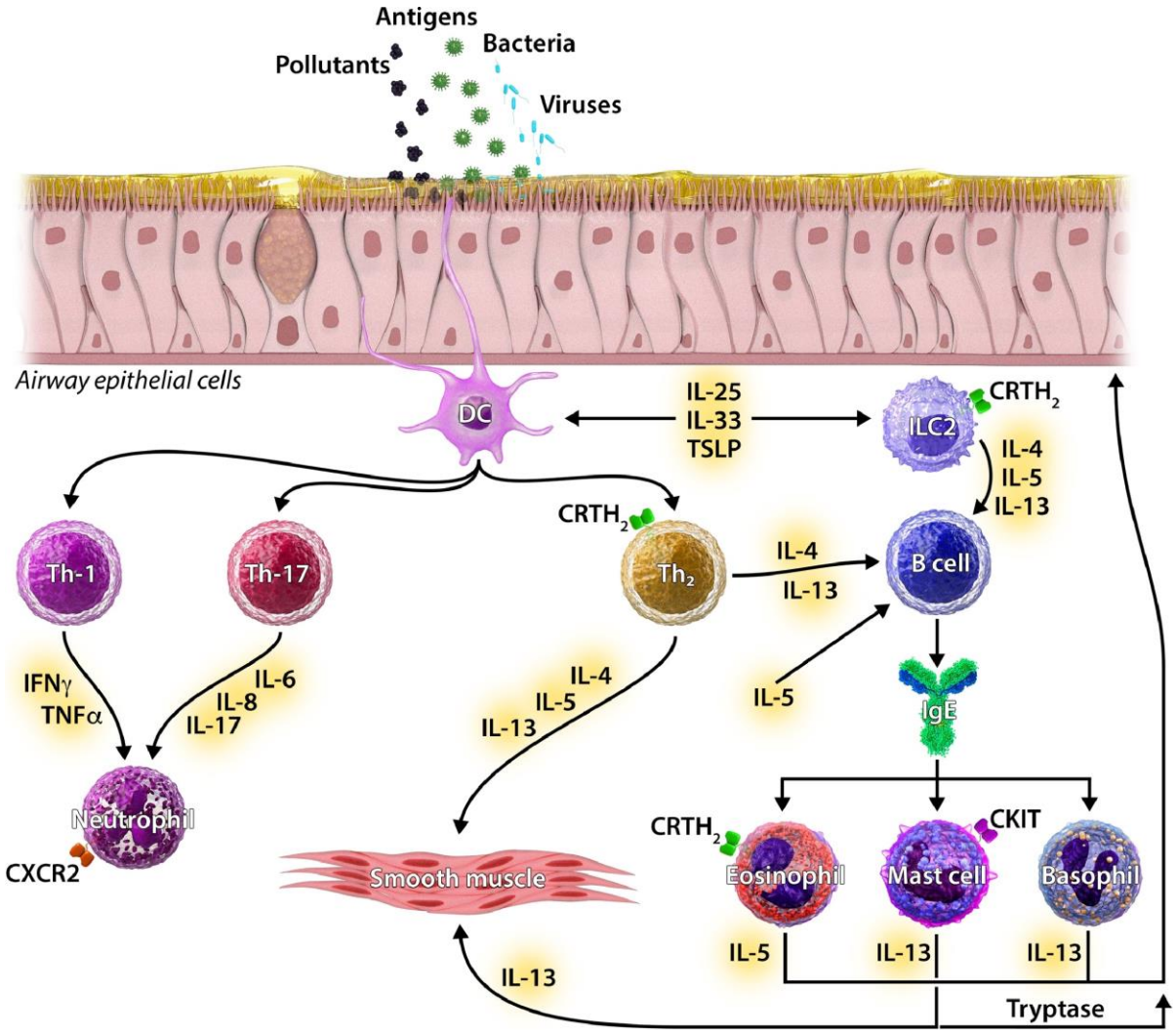
Exhaled nitric oxide (FeNO)

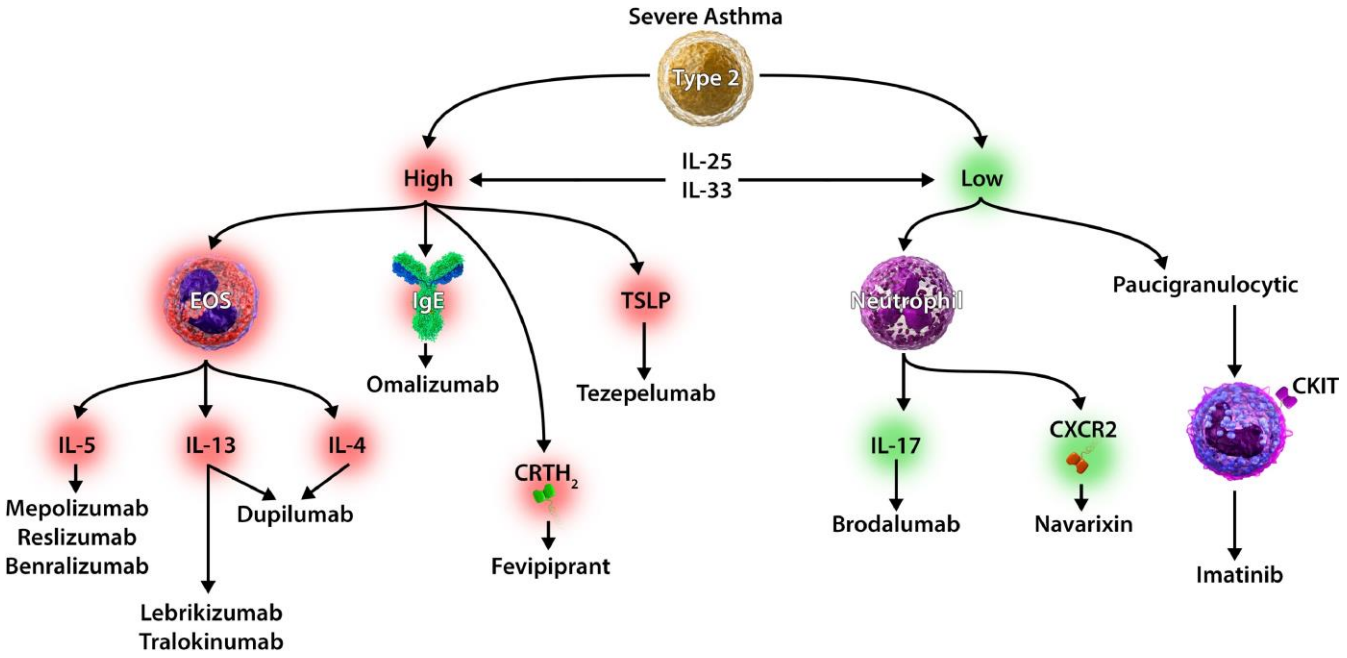
- FeNO-guided treatment
  - Updated to reflect new meta-analyses *(Petsky Cochrane 2016; Petsky Cochrane 2016)* that separately analyzed studies in which the control algorithm was reasonably close to current clinical recommendations, and therefore provided a clinically relevant comparator
  - Children/adolescents: FENO-guided treatment was associated with significantly fewer exacerbations and lower exacerbation rate than treatment based on current guidelines
  - Adults: no significant difference in exacerbations with FENO-guided treatment compared with treatment based on current guidelines
  - FeNO-guided treatment is not recommended for the general asthma population at present
  - Further studies are needed to identify the populations most likely to benefit, and the optimal frequency of monitoring

TABLE I. Proposed relationship between asthma phenotypes and endotypes: asthma phenotypes can be present in more than 1 endotype, and endotypes can contain more than 1 phenotype

Phenotype:	Eosinophilic asthma
	Endotypes: allergic asthma (adult),* aspirin-sensitive asthma, severe late-onset hypereosinophilic asthma,* ABPM*
Phenotype:	Exacerbation-prone asthma
	Endotypes: allergic asthma (adult),* aspirin-sensitive asthma,* late-onset hypereosinophilic asthma, API-positive preschool wheezer,* ABPM,* viral-exacerbated asthma, premenstrual asthma
	Phenotype: Obesity-related asthma
	Endotypes: airflow obstruction caused by obesity, severe steroid-dependent asthma, severe late-onset hypereosinophilic asthma*
Phenotype:	Exercise-induced asthma
	Endotypes: cross-country skiers' asthma, other forms of elite-athlete asthma, allergic asthma, API-positive preschool wheezer*
Phenotype:	Adult-onset asthma
	Endotypes: aspirin-sensitive asthma,* infection-induced asthma, severe late-onset hypereosinophilic asthma*
Phenotype:	Fixed airflow limitation
	Endotypes: noneosinophilic (neutrophilic) asthma
Phenotype:	Poorly steroid-responsive asthma
	Endotypes: noneosinophilic (neutrophilic) asthma, steroid-insensitive eosinophilic asthma, airflow obstruction caused by obesity

*Proposed endotypes that appear in Table II.





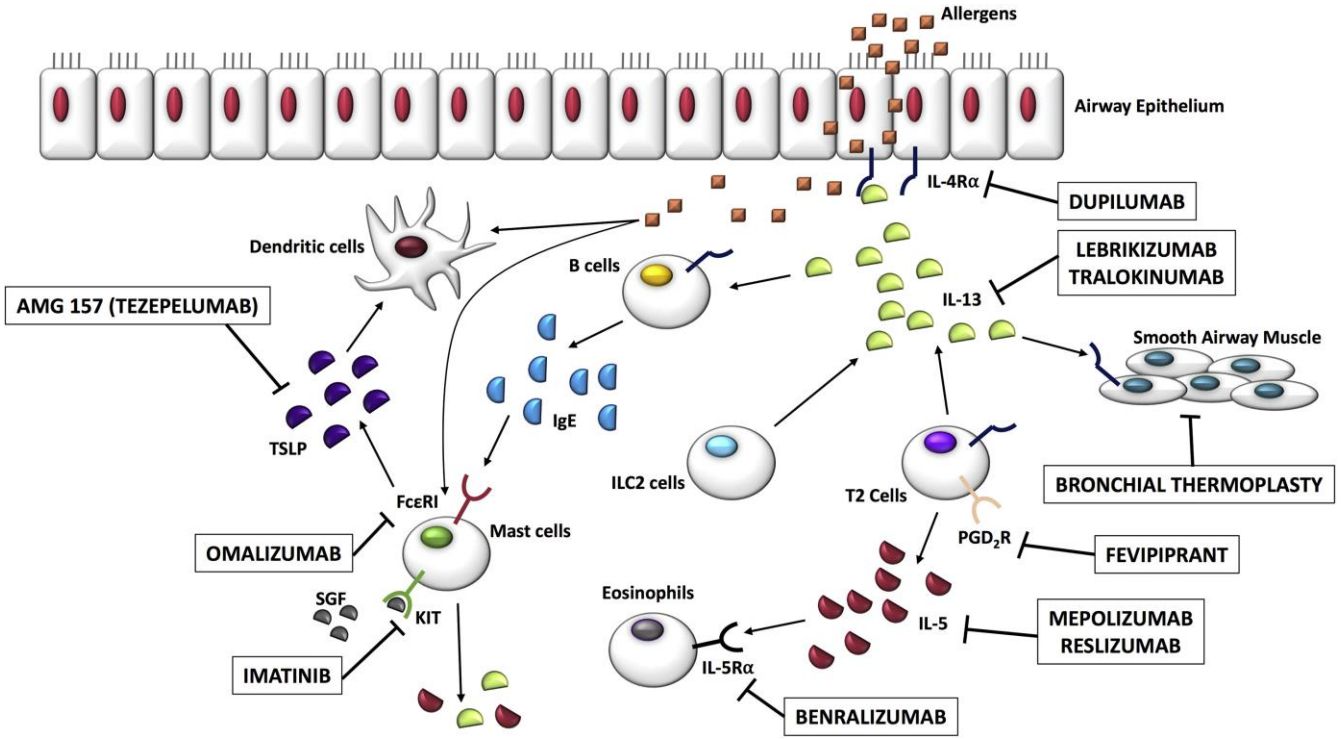
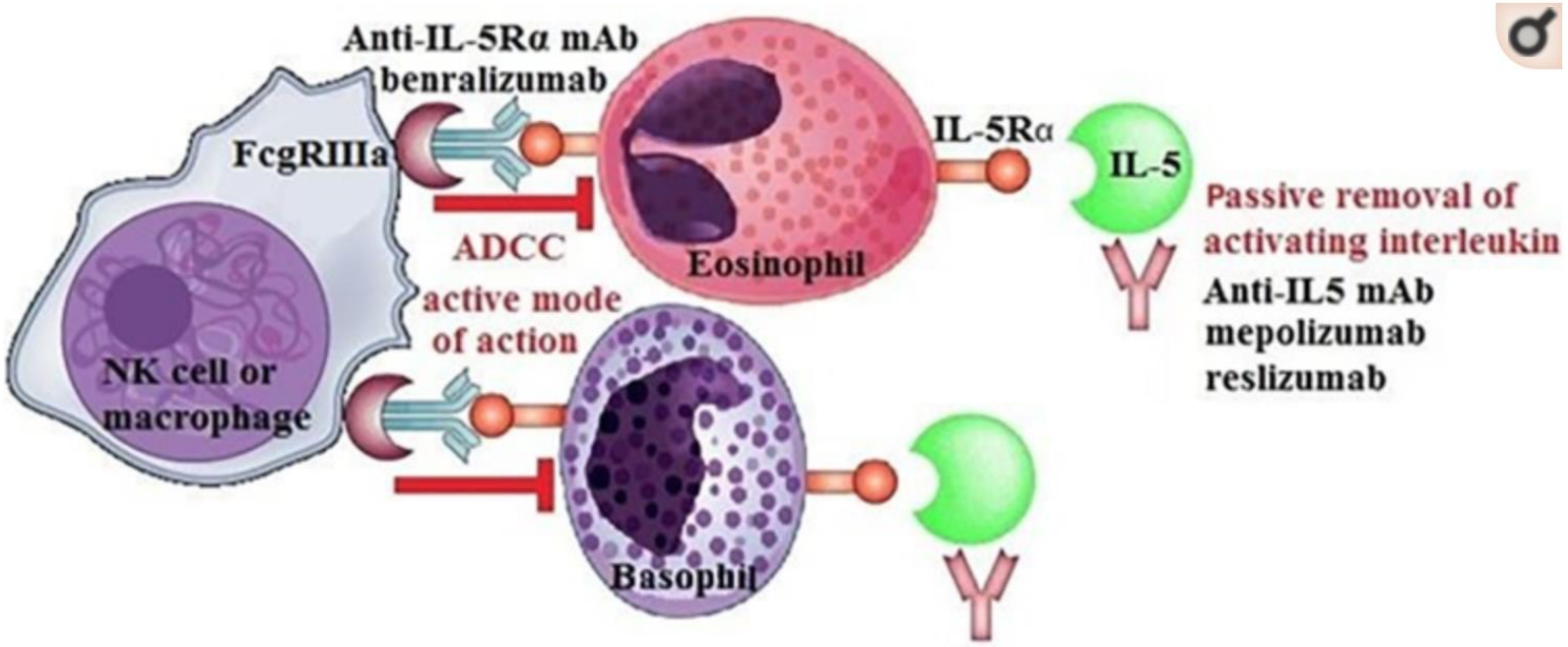


Figure 2



The mechanism of action of therapies targeting IL-5 and its receptor.

Abbreviations: IL, interleukin; ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer; mAB, monoclonal antibody.

Table 3. Summary of Adverse Events.*

Variable	Placebo (N = 191)	Mepolizumab	
		Intravenous (N = 191)	Subcutaneous (N = 194)
	number of patients (percent)		
All adverse events	158 (83)	161 (84)	152 (78)
Nonasthma event	157 (82)	161 (84)	152 (78)
Worsening of asthma	29 (15)	18 (9)	13 (7)
Drug-related event, per investigator assessment†	30 (16)	33 (17)	39 (20)
Leading to study withdrawal	4 (2)	0	1 (1)
Serious adverse events			
During treatment	27 (14)	14 (7)	16 (8)
Drug-related event, per investigator assessment†	1 (1)	0	1 (1)
Fatal	1 (1)	0	0
Most common adverse events‡			
Nasopharyngitis	46 (24)	45 (24)	33 (17)
Headache	33 (17)	46 (24)	39 (20)
Upper respiratory tract infection	27 (14)	22 (12)	24 (12)
Sinusitis	18 (9)	11 (6)	18 (9)
Bronchitis	18 (9)	14 (7)	9 (5)
Oropharyngeal pain	15 (8)	12 (6)	7 (4)
Injection-site reaction	6 (3)	5 (3)	17 (9)

* A more detailed listing of adverse events is provided in Table S4 in the Supplementary Appendix.
† The status was assigned by investigators while they were unaware of the study-group assignments.
‡ The most common adverse events were those that were reported in at least 5% of the patients in any study group.

Close Window

Table I

Proposed relationship between asthma phenotypes and endotypes: asthma phenotypes can be present in more than 1 endotype, and endotypes can contain more than 1 phenotype

Table I Proposed relationship between asthma phenotypes and endotypes: asthma phenotypes can be present in more than 1 endotype, and endotypes can contain more than 1 phenotype

Phenotype:	Eosinophilic asthma
Endotypes: allergic asthma (adult),** aspirin-sensitive asthma, severe late-onset hypereosinophilic asthma,** ABPM**	
Phenotype:	Exacerbation-prone asthma
Endotypes: allergic asthma (adult),** aspirin-sensitive asthma,** late-onset hypereosinophilic asthma, API-positive preschool wheezer,** ABPM,** viral-exacerbated asthma, premenstrual asthma	
Phenotype: Obesity-related asthma	
Endotypes: airflow obstruction caused by obesity, severe steroid-dependent asthma, severe late-onset hypereosinophilic asthma**	
Phenotype:	Exercise-induced asthma
Endotypes: cross-country skiers' asthma, other forms of elite-athlete asthma, allergic asthma, API-positive preschool wheezer**	
Phenotype:	Adult-onset asthma
Endotypes: aspirin-sensitive asthma,** infection-induced asthma, severe late-onset hypereosinophilic asthma**	
Phenotype:	Fixed airflow limitation
Endotypes: noneosinophilic (neutrophilic) asthma	
Phenotype:	Poorly steroid-responsive asthma
Endotypes: noneosinophilic (neutrophilic) asthma, steroid-insensitive eosinophilic asthma, airflow obstruction caused by obesity	

*Proposed endotypes that appear in Table II .

Table 2
Biomarkers Can Perform Multiple Functions toward Diagnosis and Treatment of Severe Asthma

Biomarker	Diagnostic	Predictive	Dynamic	Stable
IgE		x	x	
Specific IgE	x			
Eosinophils	x	x	x	
Neutrophils	x			
Fraction of exhaled nitric oxide		x	x	
Eosinophil peroxidase	x	x	x	
Bromotyrosine	x	x	x	
Stem cell factor/KIT		x		
Urinary leukotriene E4	x	x	x	
Periostin		x		
Single nucleotide polymorphisms		x		x

Abbreviations: IgE, immunoglobulin E; KIT, proto-oncogene receptor tyrosine kinase.

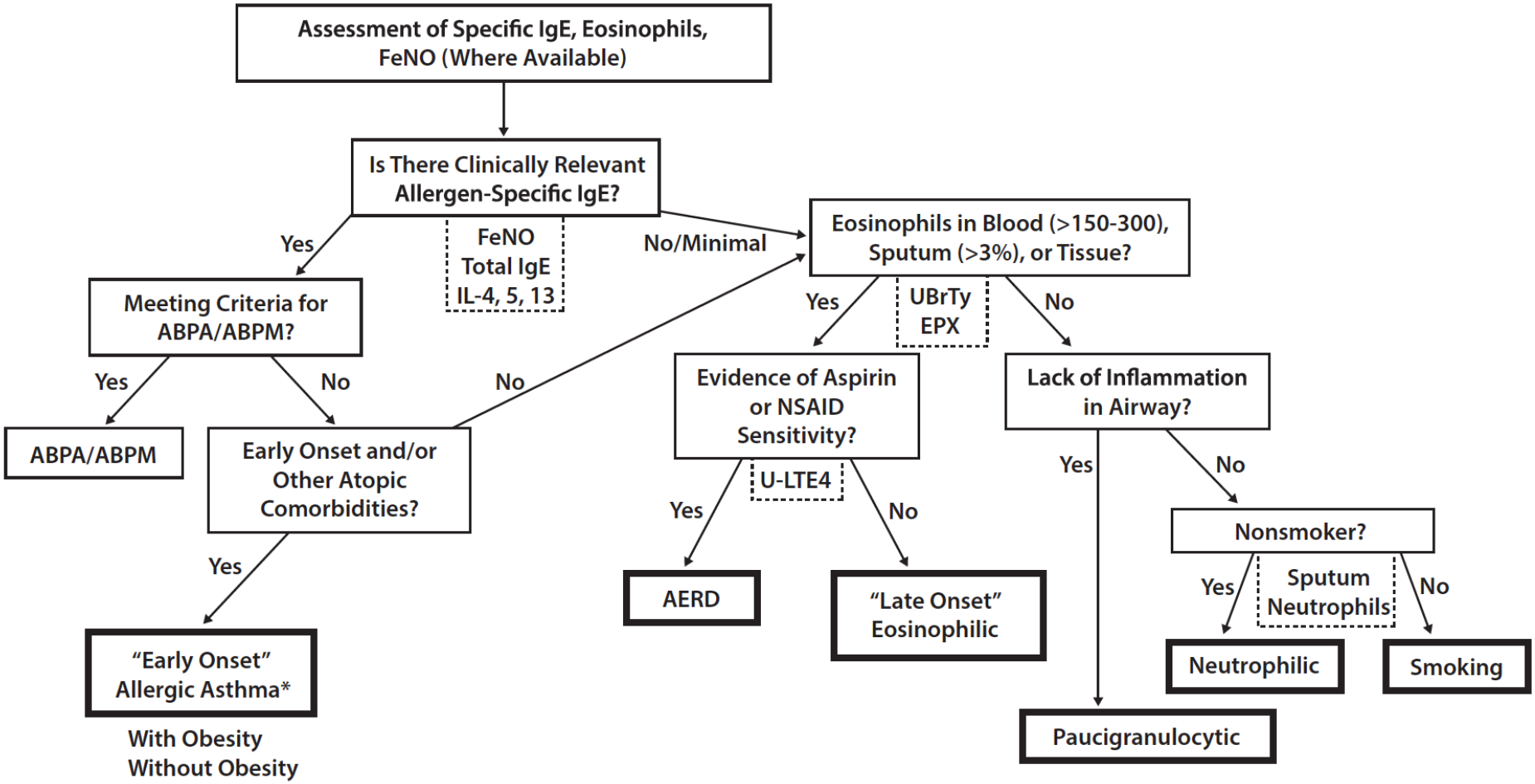


Figure 1. Biomarker-based approach to identifying phenotypes and endotypes of severe asthma. Dashed lines indicate accessory biomarkers. ABPA: Allergic bronchopulmonary aspergillosis; ABPM: Allergic bronchopulmonary mycosis; AERD: aspirin-exacerbated respiratory disease; UBrTy: urinary bromotyrosine; EPX: eosinophil peroxidase; FeNO: Fraction of exhaled nitric oxide; U-LTE4: Urinary leukotriene E4. *May be childhood or adult onset.

TABLE II. Examples of endotypes that fulfill at least 5 of 7 prespecified disease characteristics

Endotype of the asthma syndrome	Disease characteristics							
	Clinical characteristics	Biomarkers	Lung physiology	Genetics	Histopathology	Epidemiology	Treatment response	Proposed mechanism
Proposed endotype	History, physical examination, comorbidities	Eosinophilia, FeNO, SPT, IgE	BHR, FEV_1, reversibility	SNPs and pathways	Tissue/lung characteristics	Prevalence, risk factors, and natural history	Response or lack of response to a specific treatment	Specific biological pathway or process
Aspirin-sensitive asthma	Polyposis, often more severe asthma	Often eosinophilic, increased urinary LTs	Response to aspirin challenge	LT-related gene polymorphisms	Often eosinophilic	Adult onset, severe disease poor prognosis, prevalence 2% to 5%	Responds to anti-LT, especially 5-LO inhibitors	Likely eicosanoids-related
ABPM	Severe, mucus production, adult/long disease duration	Blood eosinophilia, markedly elevated IgE and specific IgE	Less reversible/fixed airflow obstruction	HLA and rare CF variants	Bronchiectasis/ eosinophils and PMNs, bronchocentric granulomatosis	Long duration/ adult onset/poor prognosis	Glucocorticoids, antifungals, possibly omalizumab	Colonization of airways
Allergic asthma (adults)	Allergen associated symptoms/allergic rhinitis	Positive SPT, elevated IgE/ elevated FeNO	Specific allergic bronchospasm	T_H2 pathway SNPs	Eosinophils, SBM thickening	Childhood onset, history of eczema	Responds to glucocorticoids and omalizumab, possible IL-4/13 pathway inhibition	T_H2–dominant
API-positive preschool wheezer	>3 episodes per year, 1 major or 2 minor characteristics	Often >4% eosinophils in blood (minor), aeroallergen-specific IgE	Potential increased risk of loss of lung function	Unknown	Unknown	Mother or father with asthma	Responds well to daily inhaled glucocorticoids	T_H2–dominant
Severe late-onset hypereosinophilic	Severe exacerbations, late-onset disease	Peripheral blood eosinophilia	Bronchodilator–resistant, episodic fall in lung function, steroid–sensitive	No evidence	High blood eosinophil count and eosinophils in tissue	Approximately 20% of severe asthma populations	Glucocorticoid-sensitive, often oral steroid–dependent, responds to anti–IL-5	Nonatopic, otherwise unknown
Asthma in cross-country skiers	Mild to moderate severity, symptoms mostly related to exercise, URTI commonly reported	FeNO normal, normal blood eosinophil count, increased LTE_4 in urine	Methacholine and or exercise positive, usually negative to mannitol or AMP challenge	Unknown	SBM thickening with low-grade noneosinophilic inflammation, increased neutrophils in sputum related to training intensity or duration, BALT in airway mucosa	15% to 25% of elite skiers, highest prevalence among those training in a cold, dry environment	Responds poorly to inhaled glucocorticoid treatment, improves when training intensity diminishes	Cold, dry air induces chronic stress to the airways, subclinical viral infections?

BALT, Bronchus-associated lymphoid tissue; *BHR,* bronchial hyperresponsiveness; *CF,* cystic fibrosis; *FeNO,* fractional exhaled nitric oxide; *LT,* leukotriene; *LTE_4,* leukotriene E_4; *5-LO,* 5-lipoxygenase; *SBM,* subepithelial basement membrane; *SNP,* single nucleotide polymorphism; *SPT,* skin prick test; *URTI,* upper respiratory tract infection.

- Among participants with eosinophilic granulomatosis with polyangiitis, 32% had remission at weeks 36 and 48 when treated with mepolizumab, an anti–interleukin-5 monoclonal antibody, as compared with 3% of the participants in the placebo group.

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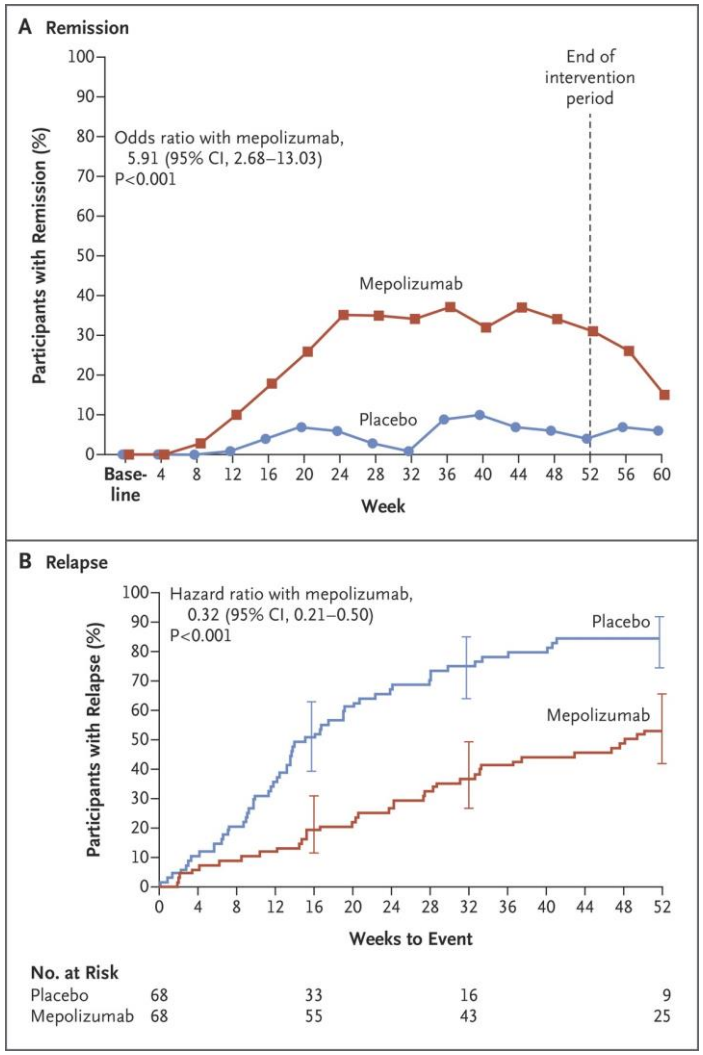


Mepolizumab
(Nucala)

for severe asthma: 100mg subcutaneous every 4 weeks
for eosinophilic granulomatosis with polyangiitis: 300mg every 4 weeks

Hypersensitivity reactions have occurred generally within hours of the injection.

During trials, Herpes zoster was noted in several patients, consider vaccination.

Helminth infections may be a problem, treat it and consider stopping the mepolizumab.

Injection site reactions were present in 8% versus 3% in placebo patients.

No mention of an eosinophil count that would indicate eosinophilic phenotype.

Reslizumab
(Cinqair)

IV infusion over 20-50 minutes
3mg/kg every 4 weeks
anaphylaxis was 0.3%
eosinophil counts >400 was in their studies
malignancy 6/1028 (0.6%) versus 2/730 placebo patients (0.3%)

Benralizumab
(Fasenra)

Age 12 and older
Comes in a syringe for subcutaneous injection
30mg every 4 weeks for first 3 doses followed by once every 8 weeks thereafter
Study of steroid reduction that permitted majority of patients to reduce their steroids as compared to reducing the exacerbation rate
Headache was in 8% versus 6% of placebo patients
Concern about hypersensitivity reactions although nothing as yet has been validated

Dupilumab
(Dupixent)

Hypersensitivity was in <1%
Conjunctivitis and keratitis was seen in atopic dermatitis patients.
Warning of eosinophilic conditions.
Avoid use of live vaccines.
Indication is for eosinophilic phenotype or with oral corticosteroid dependent asthma.
Self administered subcutaneous injection.
2 doses:
Initial 400mg loading dose followed by 200mg every other week.
Initial 600mg loading dose followed by 300mg every other week.

Eosinophilia can develop.

Table 1. Demographic Characteristics and Diagnostic and Baseline Characteristics of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in the Intention-to-Treat Population.*

Characteristic	Mepolizumab (N = 68)	Placebo (N = 68)
Age — yr	49±12	48±14
Male sex — no. (%)	26 (38)	30 (44)
ANCA-positive status — no. (%)†	7 (10)	6 (9)
Absolute eosinophil count per cubic millimeter‡	177±1.29	172±1.35
BVAS >0 — no. (%)§	37 (54)	48 (71)
Prednisolone or prednisone dose — mg/day		
Median	12.0	11.0
Range	7.5–40.0	7.5–50.0
Immunosuppressive therapy at baseline — no. (%)	41 (60)	31 (46)
EGPA diagnostic disease characteristics — no. (%)		
Asthma with eosinophilia	68 (100)	68 (100)
Biopsy evidence¶	25 (37)	31 (46)
Neuropathy‖	32 (47)	24 (35)
Nonfixed pulmonary infiltrates	50 (74)	48 (71)
Sinonasal abnormality	64 (94)	64 (94)
Cardiomyopathy**	13 (19)	7 (10)
Glomerulonephritis	1 (1)	0
Alveolar hemorrhage	3 (4)	1 (1)
Palpable purpura	9 (13)	8 (12)
ANCA-positive status	13 (19)	13 (19)
Relapsing disease — no. (%)	51 (75)	49 (72)
Refractory disease — no. (%)	34 (50)	40 (59)
Duration since diagnosis of EGPA — yr	5.2±4.4	5.9±4.9
Immunosuppressive therapy since diagnosis — no. (%)	56 (82)	49 (72)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. Demographic characteristics were assessed at visit 2.

† Positive antineutrophil cytoplasmic antibody (ANCA) status for myeloperoxidase or proteinase 3 was assessed by means of immunoassay performed at the Covance laboratory and Q^2 Solutions.

‡ The absolute eosinophil count is presented as geometric means with standard deviation logs.

§ The Birmingham Vasculitis Activity Score (BVAS) was assessed on a scale from 0 to 63, with higher scores indicating greater disease activity.

¶ Biopsy evidence was defined as a biopsy specimen showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation.

‖ Neuropathy was defined as mononeuropathy or polyneuropathy (motor deficit or nerve-conduction abnormality).

** The presence of cardiomyopathy was established by means of echocardiography or magnetic resonance imaging.

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Mepolizumab (N=68)	Placebo (N=68)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Primary end points				
Accrued weeks of remission over 52-wk period			5.91 (2.68–13.03)	<0.001
0 wk	32 (47)	55 (81)		
>0 to <12 wk	8 (12)	8 (12)		
12 to <24 wk	9 (13)	3 (4)		
24 to <36 wk	10 (15)	0		
≥36 wk	9 (13)	2 (3)		
Remission at wk 36 and wk 48	22 (32)	2 (3)	16.74 (3.61–77.56)	<0.001
Other end points				
Remission within the first 24 wk that was sustained until wk 52	13 (19)	1 (1)	19.65 (2.30–167.93)	0.007
First EGPA relapse	38 (56)	56 (82)	0.32 (0.21–0.50)	<0.001

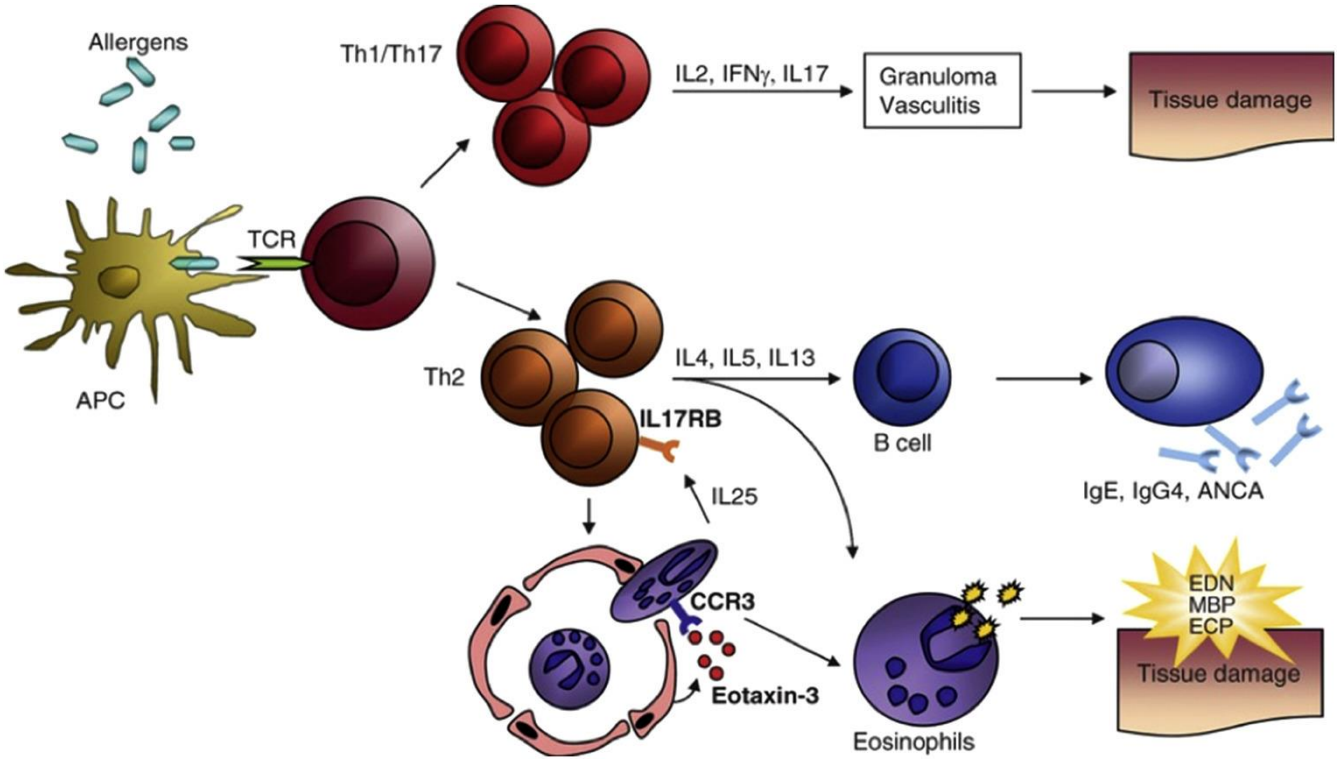
* Odds ratios are shown for the analyses of the two primary end points and for the secondary analysis of remission within the first 24 weeks that was sustained until week 52. For the analysis of accrued weeks in remission, the odds ratio is for 24 or more weeks of accrued remission. Remission was defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) and a prednisolone or prednisone dose of 4.0 mg or less per day. For the time-to-event analysis of the first relapse of EPGA, the hazard ratio is shown. Participants with a first EGPA relapse were those who had a relapse before the completion of the planned trial period or who withdrew prematurely from the trial.

Table 3. Adverse Events and Serious Adverse Events.*

Event	Mepolizumab (N=68)	Placebo (N=68)
	no. of participants (%)	
Adverse event		
Any event	66 (97)	64 (94)
Event considered by the investigator to be related to the trial agent	35 (51)	24 (35)
Event leading to trial-agent discontinuation or trial withdrawal	2 (3)	1 (1)
Death	1 (1)†	0
Serious adverse event‡		
Any event	12 (18)	18 (26)
Event considered by the investigator to be related to the trial agent	3 (4)	3 (4)
Systemic or local-site reaction§		
Systemic reaction	4 (6)	1 (1)
Local-site reaction	10 (15)	9 (13)
Anaphylaxis considered by the investigator to be related to the trial agent	0	0
Cardiovascular adverse event¶		
Arrhythmia	2 (3)	3 (4)
Stroke or TIA	1 (1)	0
Congestive heart failure	0	1 (1)
Myocardial infarction or unstable angina	1 (1)	1 (1)

* There were no significant between-group differences. TIA denotes transient ischemic attack.
† The event (cardiac arrest) was not considered by the physician to be related to the trial regimen.
‡ Serious adverse events were defined as any untoward medical occurrence that resulted in death, was life-threatening, resulted in hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, was a congenital anomaly or birth defect, or was indicative of possible drug-induced liver injury with hyperbilirubinemia.
§ Systemic or local-site reactions were identified by means of an electronic case-report form that was designed for the collection of data on systemic reactions.
¶ Cardiovascular adverse events were identified by means of an electronic case-report form that was designed for the collection of data on cardiovascular events.

- In participants with eosinophilic granulomatosis with polyangiitis, mepolizumab resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thus allowing for reduced glucocorticoid use.
- Even so, only approximately half the participants treated with mepolizumab had protocol-defined remission.


Allergens
Th1/Th17
IL2, IFNγ, IL17
Granuloma
Vasculitis
Tissue damage
TCR
APC
Th2
IL4, IL5, IL13
B cell
IgE, IgG4, ANCA
IL17RB
IL25
CCR3
Eotaxin-3
Eosinophils
EDN
MBP
ECP
Tissue damage