T2 High/T2 Low Asthma

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Disclosures

Grant support – GSK

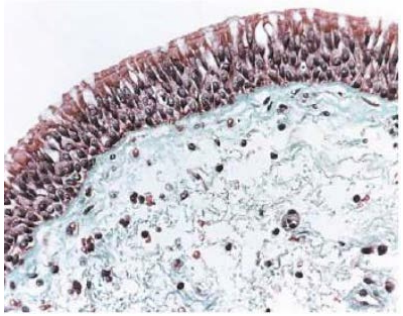
I will not be discussing off-label use for any drugs or devices

Objectives

- Appreciate the key differences between T2 high and T2 low asthma
- Using clinical characteristics and biomarkers, identify specific asthma phenotypes
- Formulate a targeted treatment plan for patients with asthma based on their ‘treatable traits’

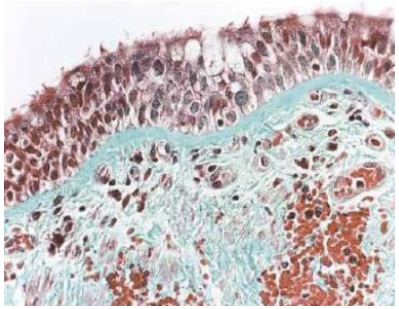
Asthma

- Heterogenous
- Chronic airway inflammation
- Wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity
- Variable expiratory airflow limitation.



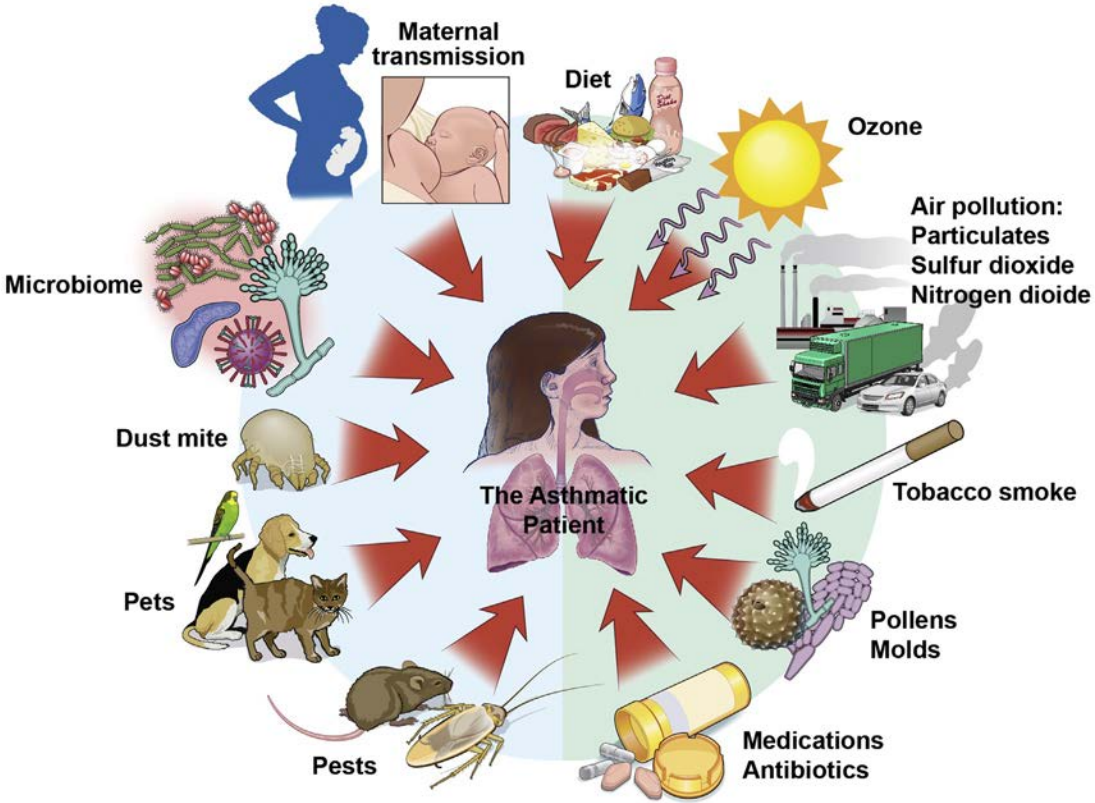
Normal

Asthma



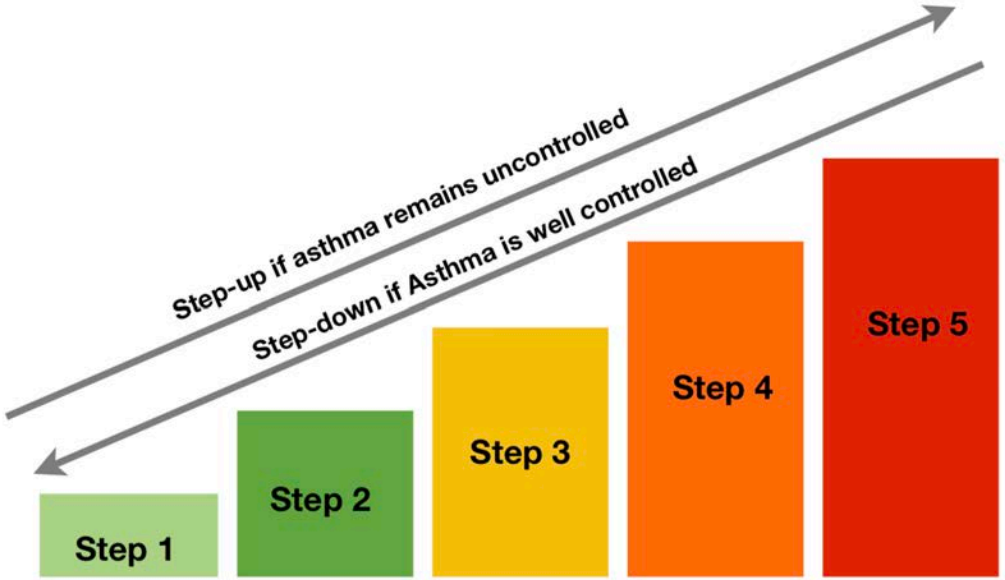
GINA 2018
Busse and Lemanske, NEJM, 2001

The Exposome & Asthma

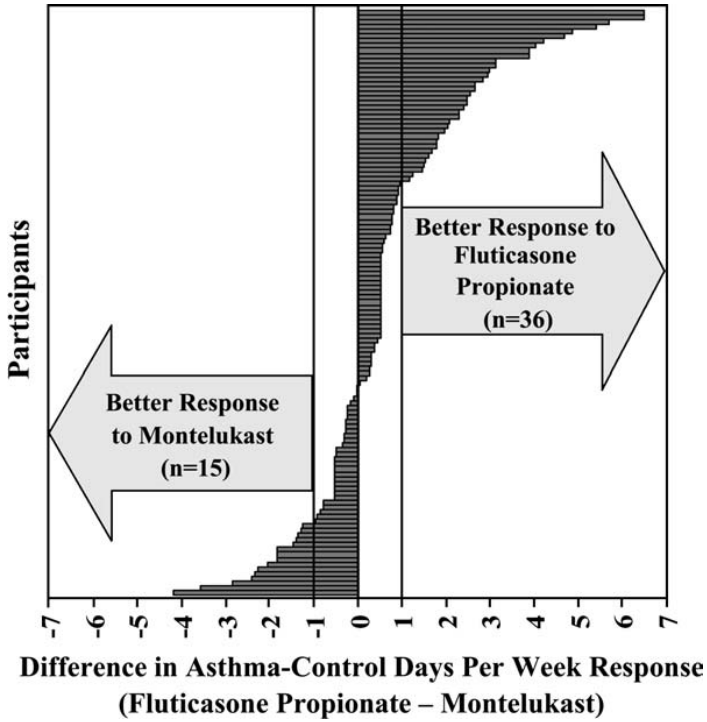


Subramanian & Khatri. Clin Chest Med 40 (2019) 107–123

Guidelines recommend stepwise approach to treatment of all asthma

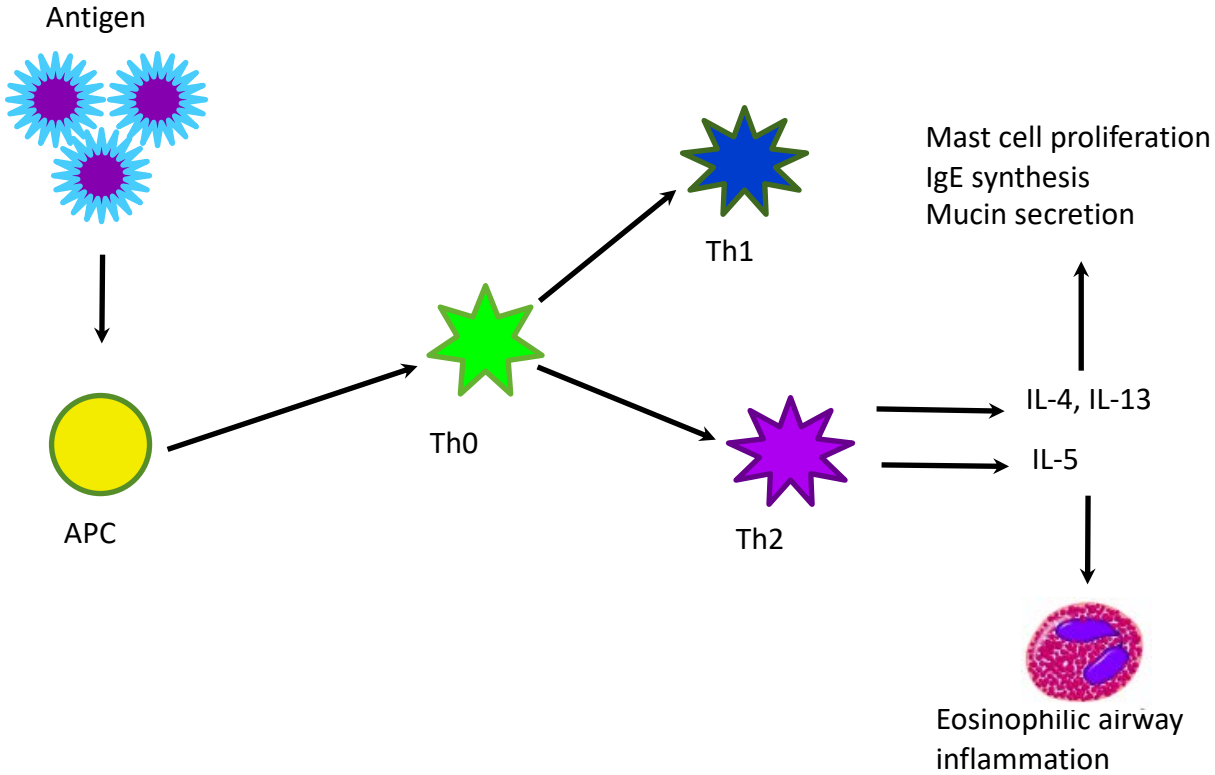


But…do not account for variability in response to medication

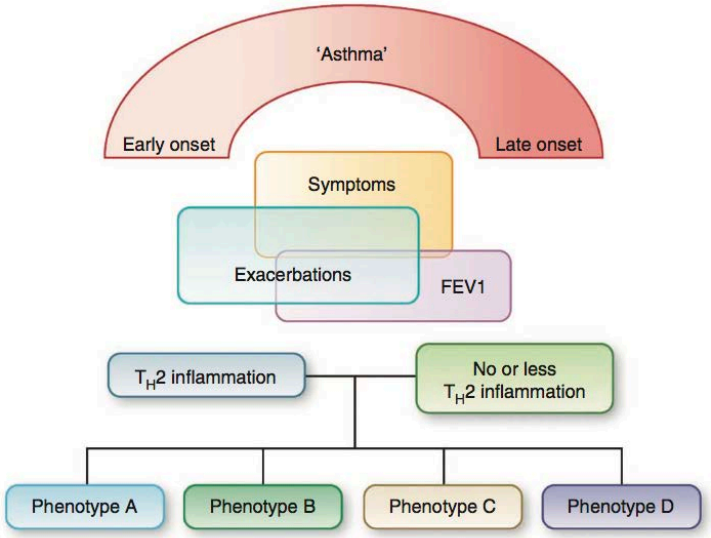


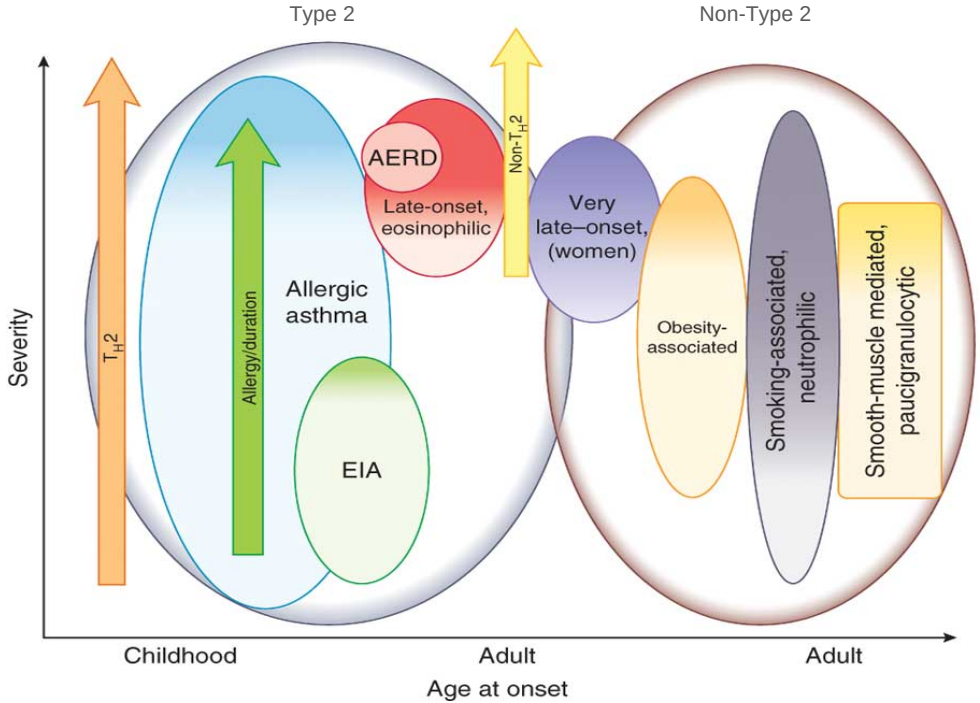
Zeiger RS. J Allergy Clin Immunol. 2006; 117: 45-52

Old Paradigm: Asthma = Th2 disease



Complex gene/environment interactions result in different clinical expressions





Wenzel Nature Medicine 2012

Question

You evaluated the following patients in clinic last week and have requested testing to better characterize their asthma. Which ONE of your patients is UNLIKELY to have non-eosinophilic asthma?

- A 56 year old female with adult onset asthma, obesity and GERD
- A 45 year old male current smoker with late onset asthma and recurrent bronchitis
- A 32 year old female nonsmoker with asthma, nasal polyps and aspirin sensitivity
- A 63 year old female nonsmoker with late onset asthma and fixed airflow obstruction

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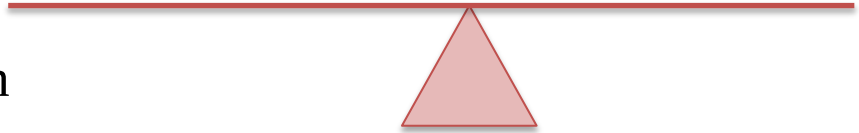


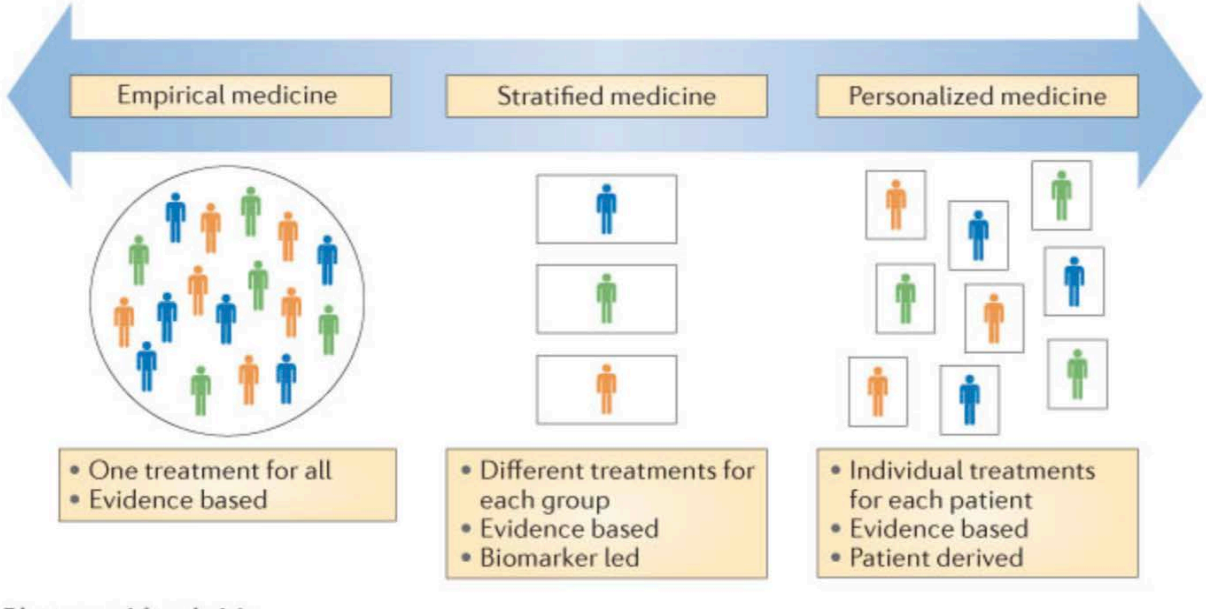
T2 High

- Allergic, atopic
- Eosinophilic
- Steroid responsive
- TH2, ILC2

T2 Low

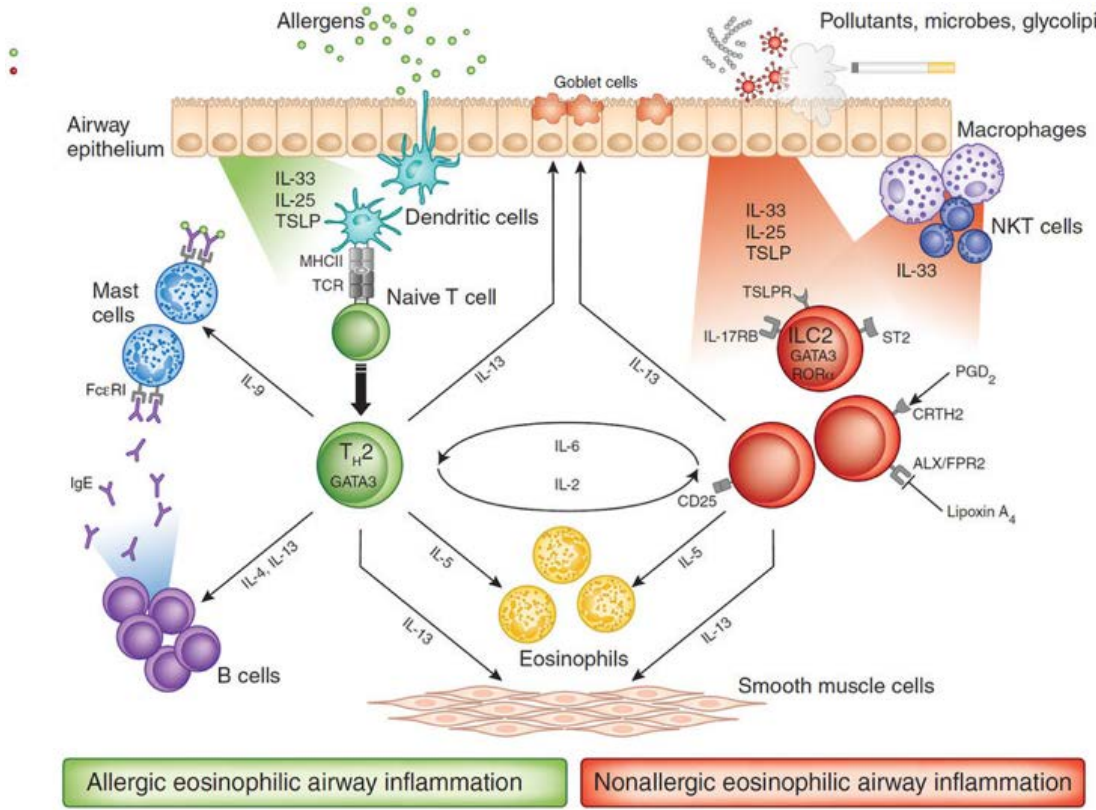
- Non-atopic
- Non-eosinophilic
- Airway remodeling
- Poorly steroid responsive
- TH1, TH17

Understanding disease mechanisms may guide a more personalized approach to therapy



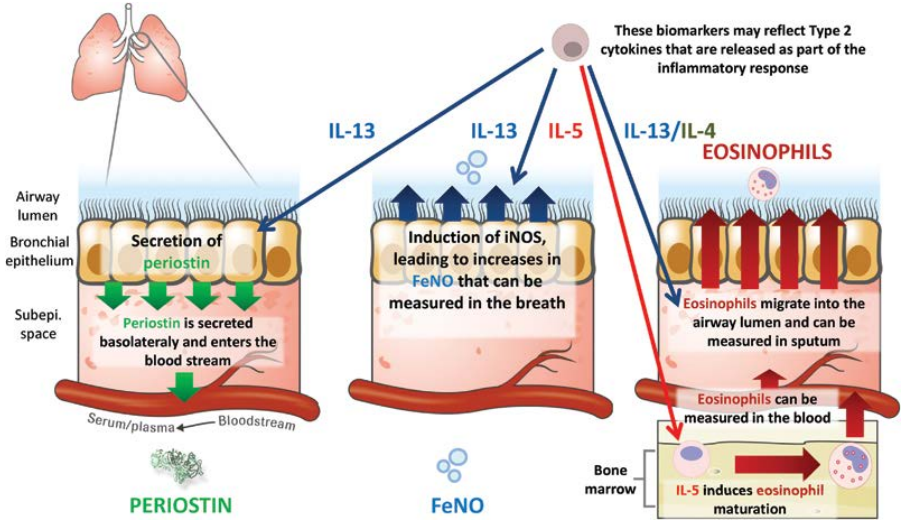
Willis JC. Nat Rev Immunol. 2015; 15: 323

Type 2 inflammation in asthma



Brusselle GG, Maes T, Bracke K. Nature Medicine 2013

Biomarkers in T2 asthma

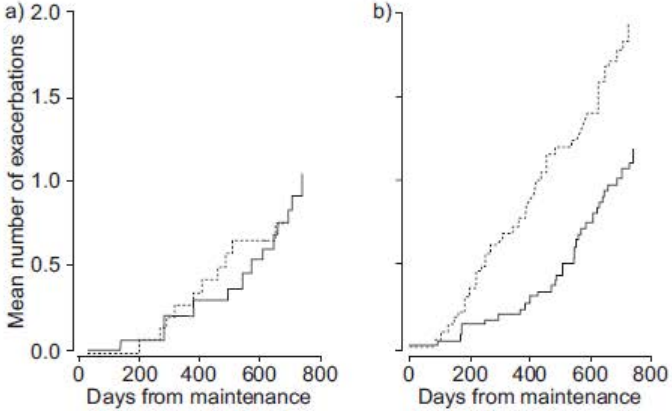


	Source	Measured characteristic	Developmental stage
Blood eosinophil	Blood	Cell (eosinophil)	Available
FeNO	Exhaled breath	Exhaled gas (nitric oxide)	Available
IgE	Blood	Protein	Available
Sputum eosinophil	Sputum	Cell (eosinophil)	Available only in specialized centers
Periostin	Blood	Protein	Unavailable
YKL-40	Blood	Protein	Research only
Transcriptomics	Blood, sputum, endobronchial biopsies	Gene	Research only
Metabolomics	exhaled breath, urine	Molecules	Research only
FD)-PET-CT	Organ	Metabolic activity uptake	Research only
Hyperpolarized gas MRI	Organ	Ventilation defects	Research only

Lim HF & Nair P. Semin Respir Crit Care Med 2018;39:56

Biomarkers are probably not necessary to manage mild asthma

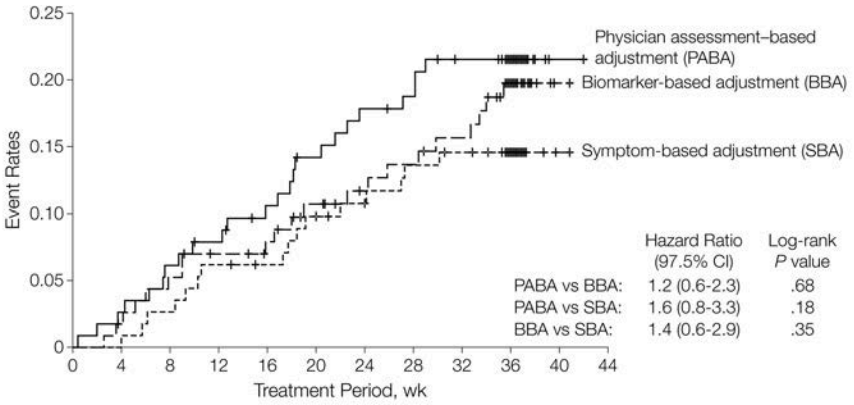
Sputum Strategy



Mild asthma

Moderate-Severe Asthma

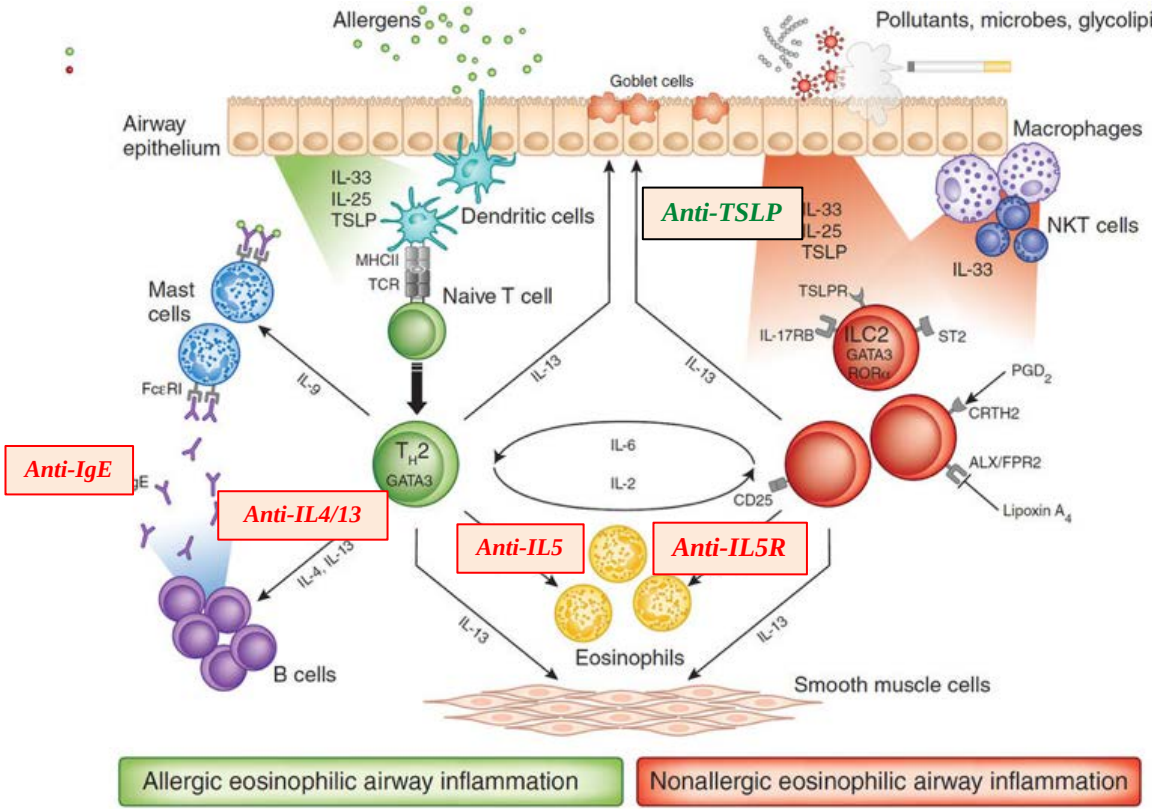
FeNO Strategy



Mild-Moderate asthma

Jayaram L. et al. ERJ 2006; 27: 483
Calhoun W et al. JAMA 2012; 308: 987

Targets for Type 2 asthma



Brusselle GG, Maes T, Bracke K. Nature Medicine 2013

Biologics for Type 2 Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®, Genentech)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens[7]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[8]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[9]
Benralizumab (Fasenra™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[10]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma[11]

ICER 2018

Biologics for Type 2 Asthma - Efficacy

Treatment	Rate Ratio (95% CI)
Omalizumab	0.52 (0.37-0.73)
Mepolizumab	0.45 (0.36-0.55)
Reslizumab	0.43 (0.33-0.55)
Benralizumab	0.59 (0.51-0.68)
Dupilumab 200 mg	0.44 (0.34-0.58)
Dupilumab 300 mg	0.40 (0.31-0.53)

Rate Ratio for exacerbations

Mean Difference AQLQ

Treatment	Difference (95% CI)
Omalizumab	0.26 (0.05-0.47)
Mepolizumab	NR
Reslizumab	0.28 (0.17-0.39)
Benralizumab	0.23 (0.11-0.35)
Dupilumab 200 mg	0.29 (0.15-0.44)
Dupilumab 300 mg	0.26 (0.12-0.40)

Treatment	Difference (95% CI)
Omalizumab	NR
Mepolizumab	-0.42 (-0.56 to -0.28)
Reslizumab	-0.27 (-0.36 to -0.19)
Benralizumab	-0.23 (-0.34 to -0.12)
Dupilumab 200 mg	-0.39 (-0.53 to -0.25)
Dupilumab 300 mg	-0.22 (-0.36 to -0.08)

Mean Difference ACQ

ICER 2018

Question

Which of the following is true about Type 2 Asthma?

A. The majority of patients with eosinophilic asthma are atopic and have early onset disease
B. AERD is a common cause of eosinophilic asthma
C. High (>2%) sputum eosinophils is noted in approximately 50% of late onset asthma
D. Eosinophilic asthma comprises at least 75% of all asthma

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Which of the following is true about Type 2 Asthma?

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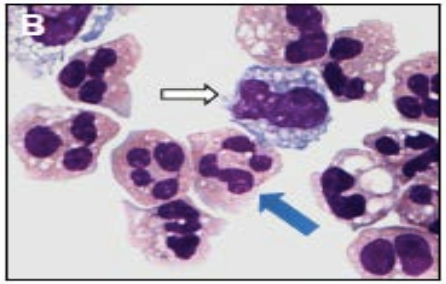
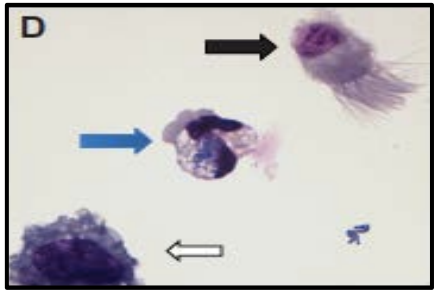
Sputum cytology

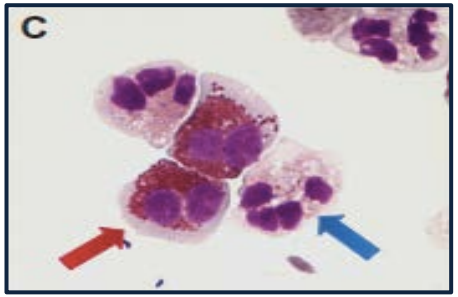
Neutrophilic



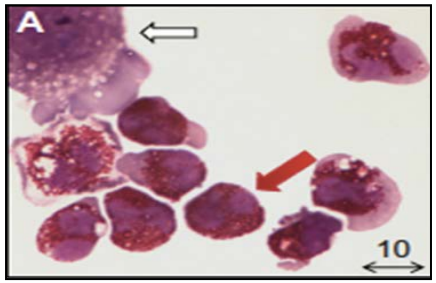
Pauci-Granulocytic



Mixed Granulocytic



Eosinophilic



- T_2 biased inflammation, using airway epithelial transcriptomics, has been observed in
  - Only 50 % of patients with mild-moderate asthma
  - Only 37% of patients with severe asthma
- Mechanisms of T2-low asthma are not well understood
  - Th1/Th17 pathway activation
  - Innate immune defects, barrier dysfunction
  - Tissue remodeling
  - Neurogenic inflammation
- Typically refractory to steroids

Woodruff P. AJRCCM 2009
Kuo CS. U-BIOPRED. AJRCCM 2017.

T2 low asthma is a common inflammatory phenotype across all severities of asthma

McGrath et al. AJRCCM 2012

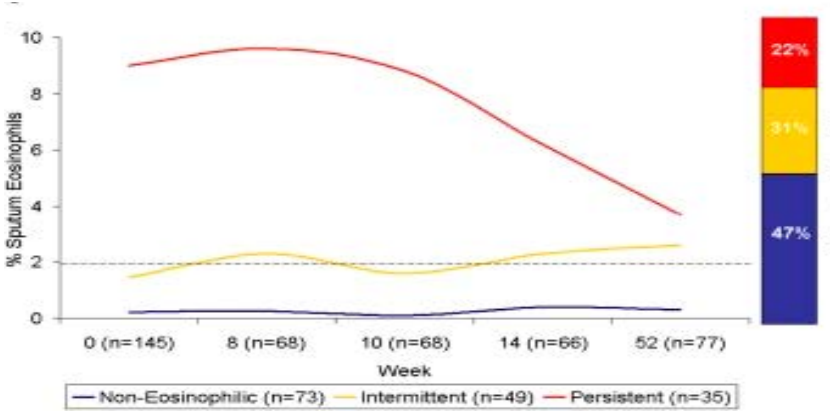
- Repeated sputum analysis from 995 subjects with **mild-mod asthma**
- 47% of patients not on ICS were persistently non-eosinophilic

Lemière et al. JACI 2006

- Sputum analysis from 31 patients with **severe asthma**
- 58% with low sputum eosinophil count (<3%)

Hastie et al. JACI 2010

- 242 patients enrolled in SARP (**Severe and Non-severe**)
- 65% had NEA (36% Paucigranulocytic; 29% neutrophilic)
- No difference between ICS+ or ICS- groups



Paucigranulocytic Asthma

Although most common phenotype in stable asthma

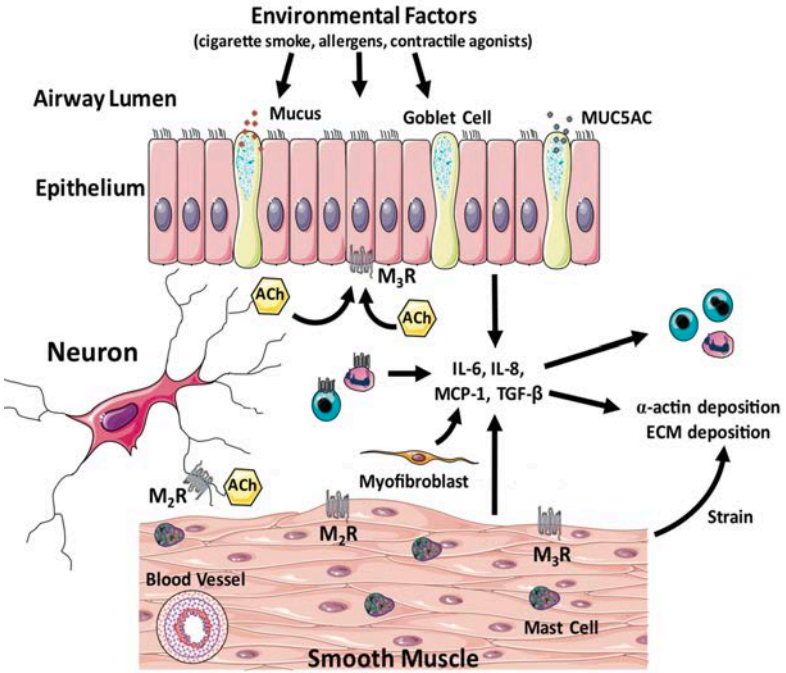
- ~20% of PGA is severe refractory

Uncoupling of airway obstruction from airway inflammation

Airway smooth muscle dysfunction and AHR

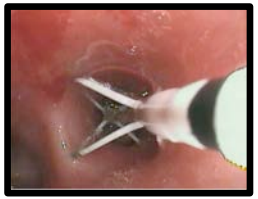
Proposed mechanisms

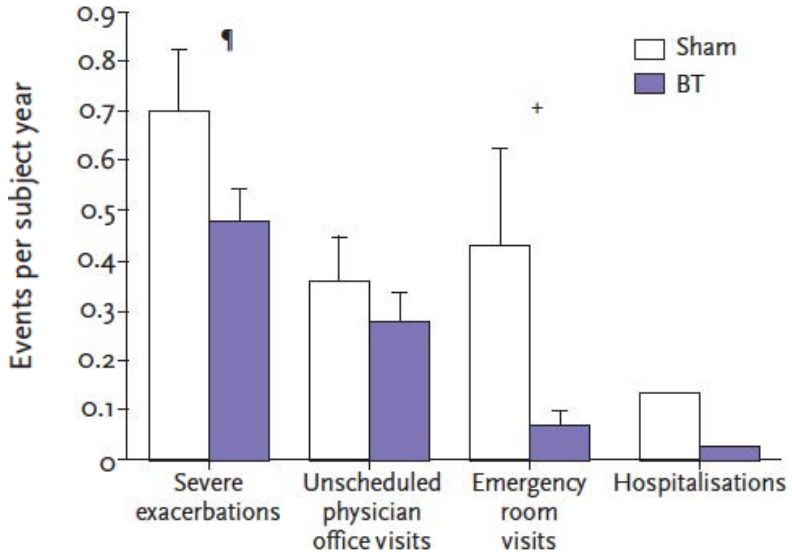
- Altered neural control of ASM contractility
- Nonimmunologic mediators & critical signaling molecules
- Upregulation of expression of specific asthma susceptible genes
- ?Consequence of 'burnout' of AI in severe longstanding asthma



Tliba and Panettieri JACI 2018

Bronchial Thermoplasty AIR2 Trial





Randomized study with sham control

Primary endpoint AQLQ

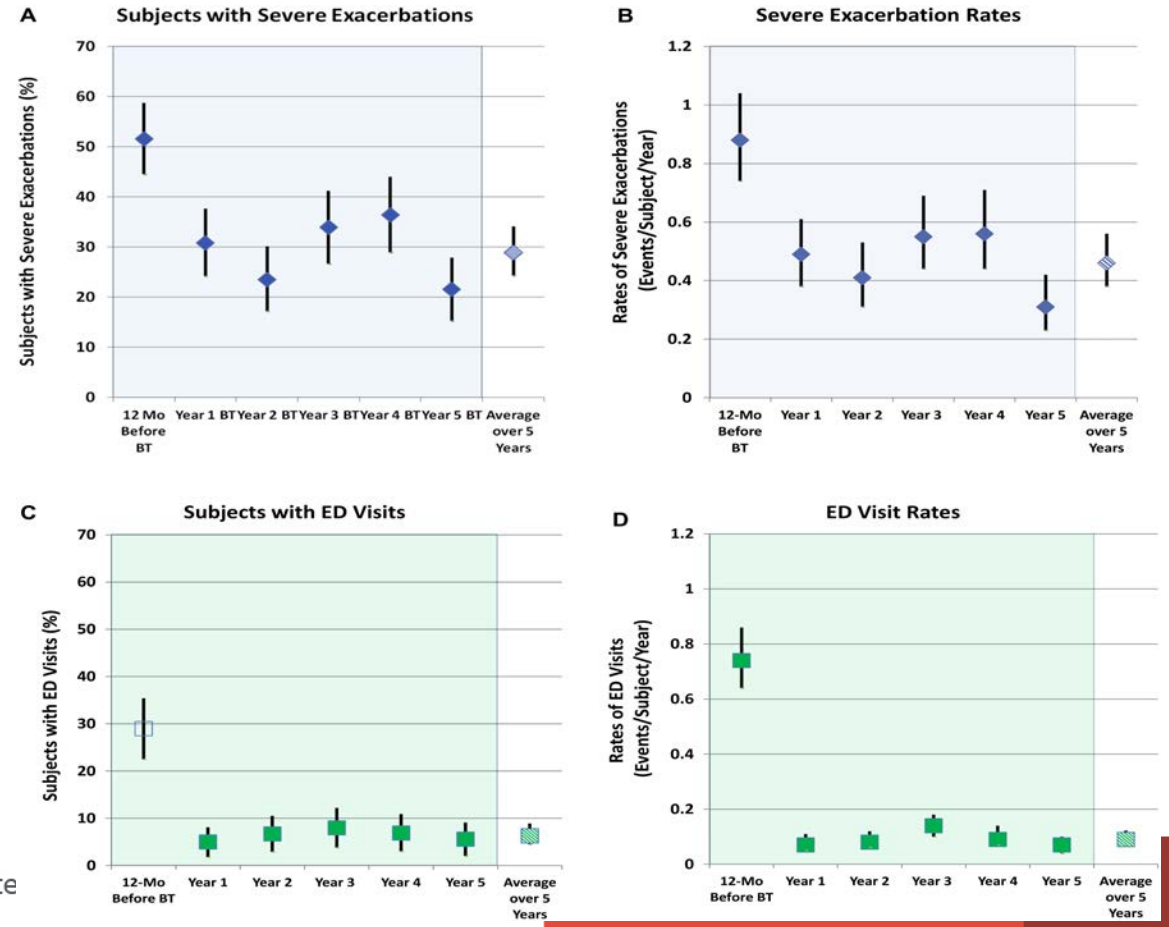
79% of BT and 64% of sham subjects achieved changes in AQLQ > 0.5

6% more BT subjects hospitalized in the treatment period (up to 6 wk after BT)

In the post-treatment period (6–52 wk after BT), the BT group had fewer severe exacerbations, ED visits

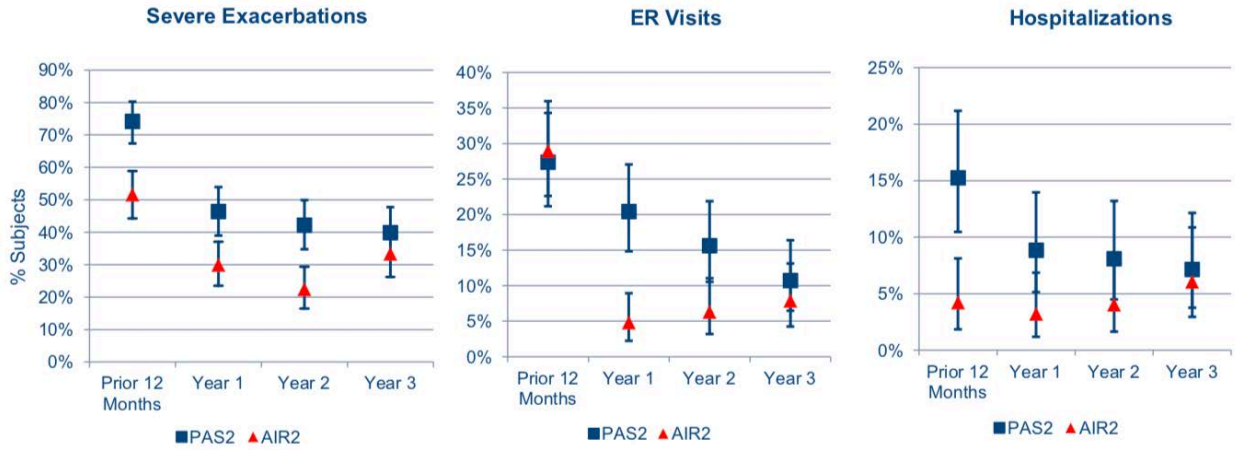
Castro M, *et al*, *Am J Respir Crit Care Med* 2010; 81 : 116

AIR2 Extension: 5-yr follow-up



Wechsler ME J Allergy Clin Immunol. 2013

Bronchial Thermoplasty PAS 2 Study
Real world effectiveness – 3 year follow-up

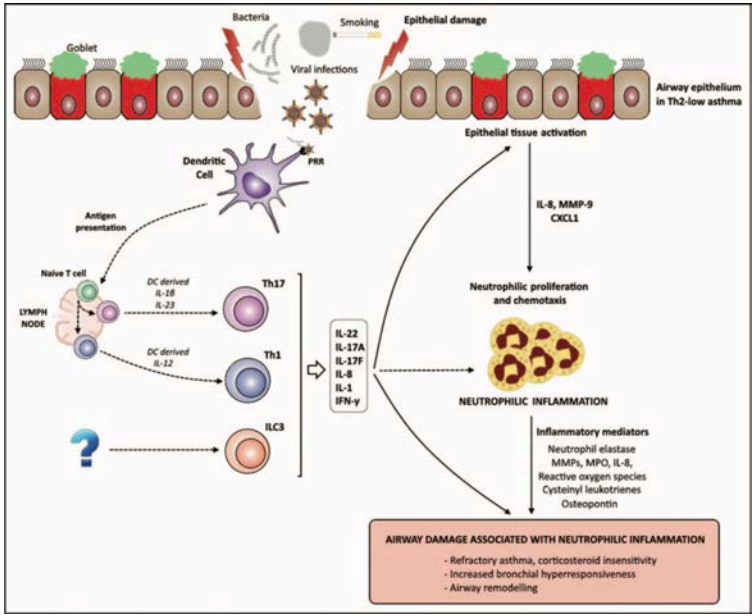


Chupp ERJ 2017

Neutrophilic Asthma

- Associated with
  - Oxidative stress
  - Chronic infection
  - Smoking
  - High fat diet

- Impaired lung function with less bronchodilator reversibility
- Increased prevalence of GERD and Chronic Rhino-Sinusitis
- Impaired Glucocorticoid response



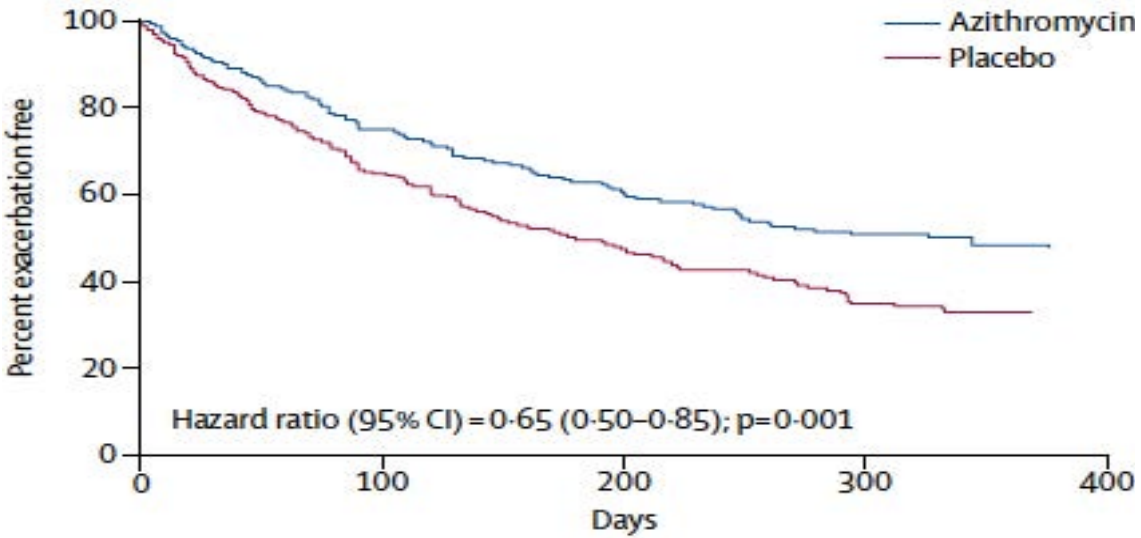
Green, R.H. et al. Thorax 2002
Simpson JL et al. Asian Pac J Allergy Immunol 2014
Samitas K. Curr Opin Pulm Med 2017

Azithromycin in asthma
AMAZES

N=420

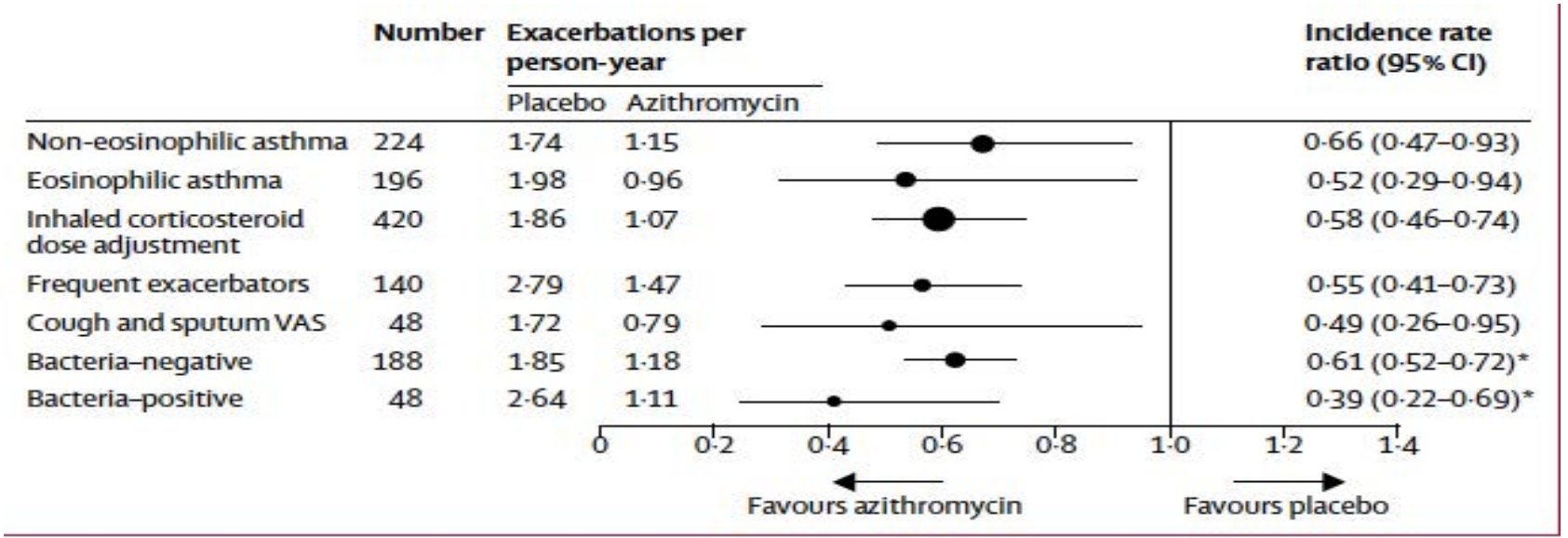
Symptomatic asthma despite ICS/LABA

Azithromycin 500 mg thrice weekly vs placebo for 48 weeks



Gibson, Peter G et al. The Lancet 2017

Azithromycin in asthma
AMAZES

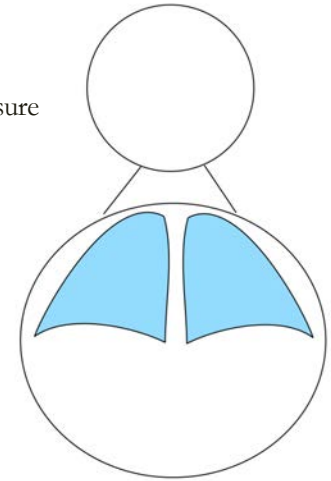


Gibson, Peter G et al. The Lancet 2017

Obesity associated asthma

Mechanical factors

Increased peripheral airway closure
Increased impedance
Mass loading
Decreased ERV



Inflammation

High fat/low fiber diet
Adipose tissue & adipokines
Innate & adaptive immune function
Gut microbiome

Comorbidities

Anxiety/Depression
GERD
OSA

Dixon AE. AJRCCM 2016

Effect of dietary weight loss on asthma in obesity

Author	Intervention	N	Weight Loss	Effect
Dias-Junior, 2014	Diet + weight loss medication	22	7.5%	Improved asthma control
Scott, 2013	Diet + exercise	28	8.5%	Improved asthma control
Hernandez Romero, 2008	Diet	96	10.6%	Improved symptoms decreased medications
	Diet		6.1%	Improved symptoms
Johnson, 2007	Diet	10	8%	Improved asthma control
Stenius-Aarniala 2000	Diet	19	14.5%	Improved lung function Improved symptoms

Which of the following cytokines is considered an “epithelial alarmin” and is being investigated as a treatment target for severe eosinophilic asthma?

A. Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF)
B. Thymic stromal lymphopoietin (TSLP)
C. Platelet-derive growth factor (PDGF)
D. Stem cell factor (SCF)

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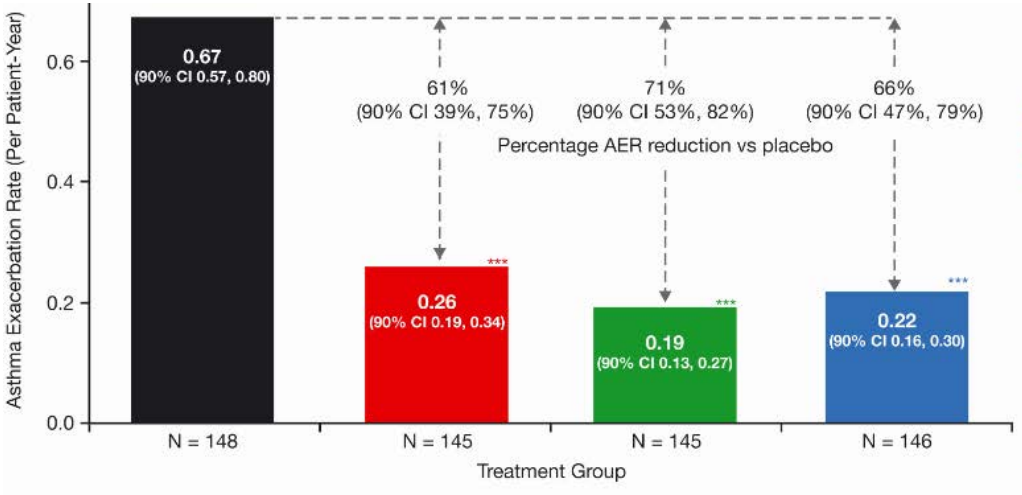
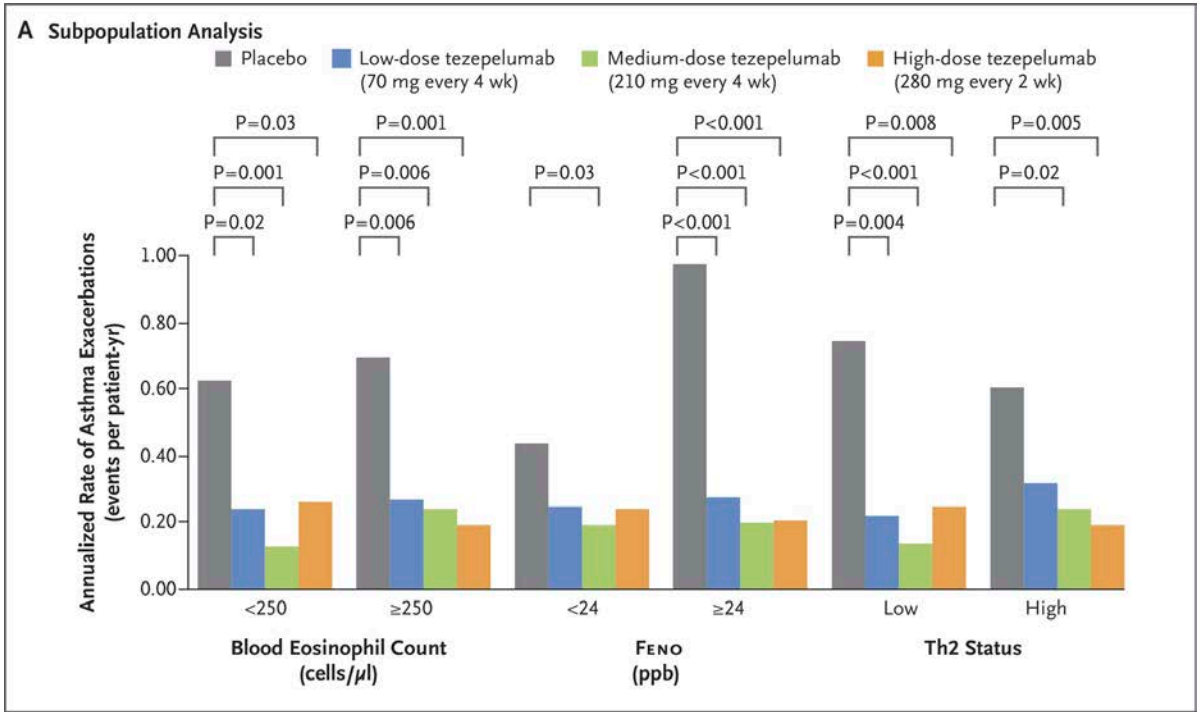
Tezepelumab in Adults with Uncontrolled Asthma

- Placebo (N = 148)
- Tezepelumab 70 mg Q4W (low-dose) (N = 145)
- Tezepelumab 210 mg Q4W (medium-dose) (N = 145)
- Tezepelumab 280 mg Q2W (high-dose) (N = 146)



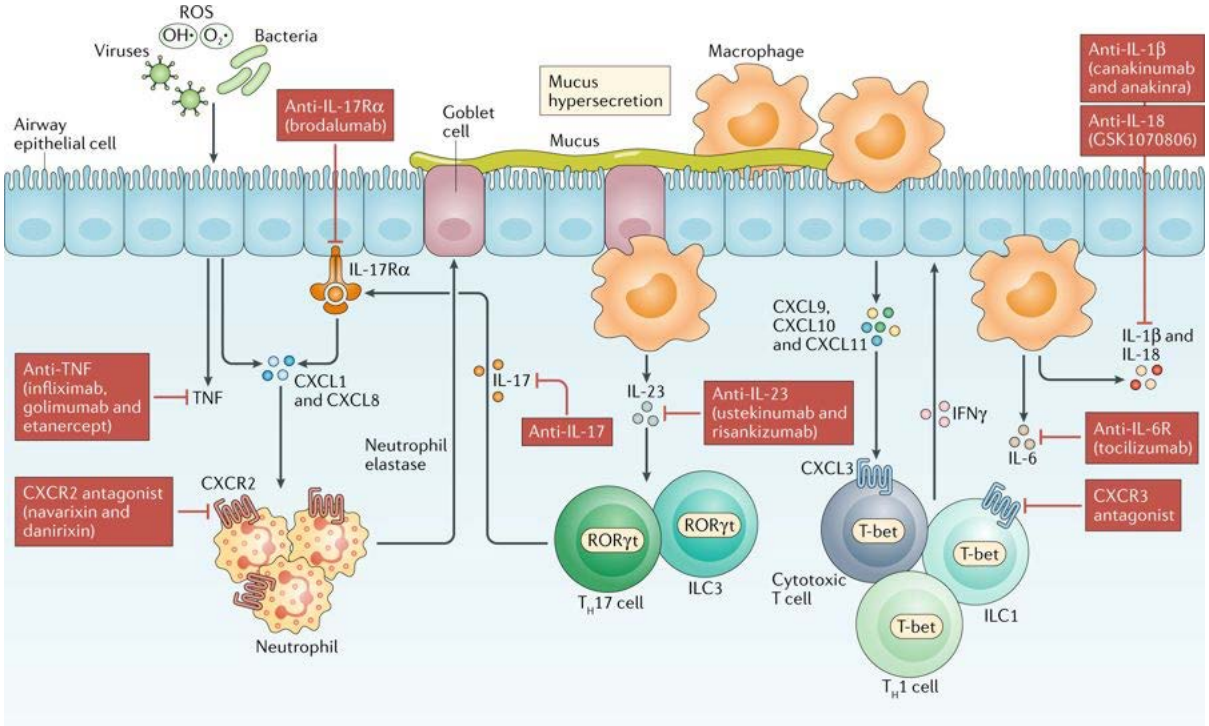
Corren J. NEJM 2017

Effect independent of Eos or Th status



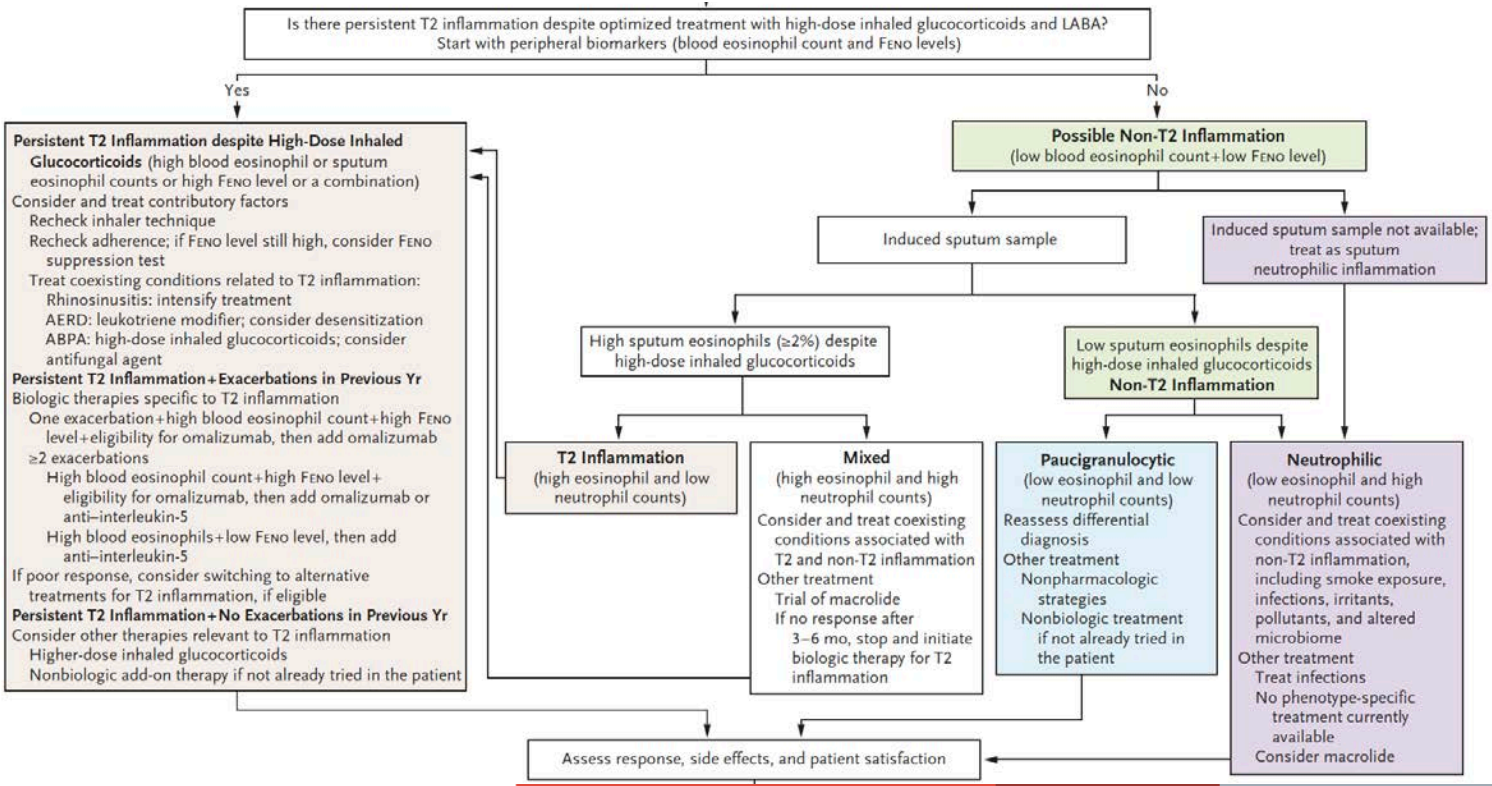
Corren J. NEJM 2017

Potential therapeutic targets in non-type 2 asthma



PJ Barnes. Nature Reviews Immunology 2018: 454–466

Proposed Treatment Approach



Israel E. NEJM 2017

Summary

- Asthma is a heterogenous disease with complex pathophysiology
- Multiple endotypes result in a myriad of phenotypes
- Eosinophilic inflammation can be allergic or non-allergic
- Current biologics target patients with T2 high asthma and biomarkers can help select most efficacious biologic
- NEoA or T2-low asthma is a common phenotype in adult asthma
- Neutrophilic inflammation is especially associated with corticosteroid-resistant severe asthma
- Urgent need for treatment options in T2 low asthma

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