Severe Asthma:
Definitions &Treatment Options

Carolyn M. Kercsmar, MD
Director, Asthma Center
Cincinnati Children's Hospital

Cincinnati Children's
changing the outcome together

Disclosure

None

Cincinnati Children's
changing the outcome together

Objectives

- Definition of severe asthma
- Pathogenesis
- Differential Diagnosis
- Treatment

Cincinnati Children's
changing the outcome together

Darryl's Asthma

- 9 year old with asthma
  - First admission age 7; now >1/year
  - 4 ED visits/year
  - Takes 4 different asthma medicines
  - Multiple triggers
  - Abnormal lung function, low FEV1

What else is going on with me?

- Lives with mom in inner city Cincinnati
- Spends weekends with dad, aunt and grandma
- Trouble getting medicines due to insurance changes
- Forgets to take medicines some days
- Apartment is very old, dusty and moldy

Is this severe asthma?

Cincinnati Children's
changing the outcome together

ATS-ERS* Severe Asthma

- The requirement for treatment with high-dose ICS** and a second controller medication (or systemic steroids>50% yr)
  - patients may or may not maintain asthma control, with this treatment regimen
- 5% of asthmatics are severe
- Severe asthma is heterogeneous

*American Thoracic Society – European Respiratory Society
** inhaled corticosteroid

Eur Respir J 2014;43:343–373.

Cincinnati Children's
changing the outcome together

Severe Asthma

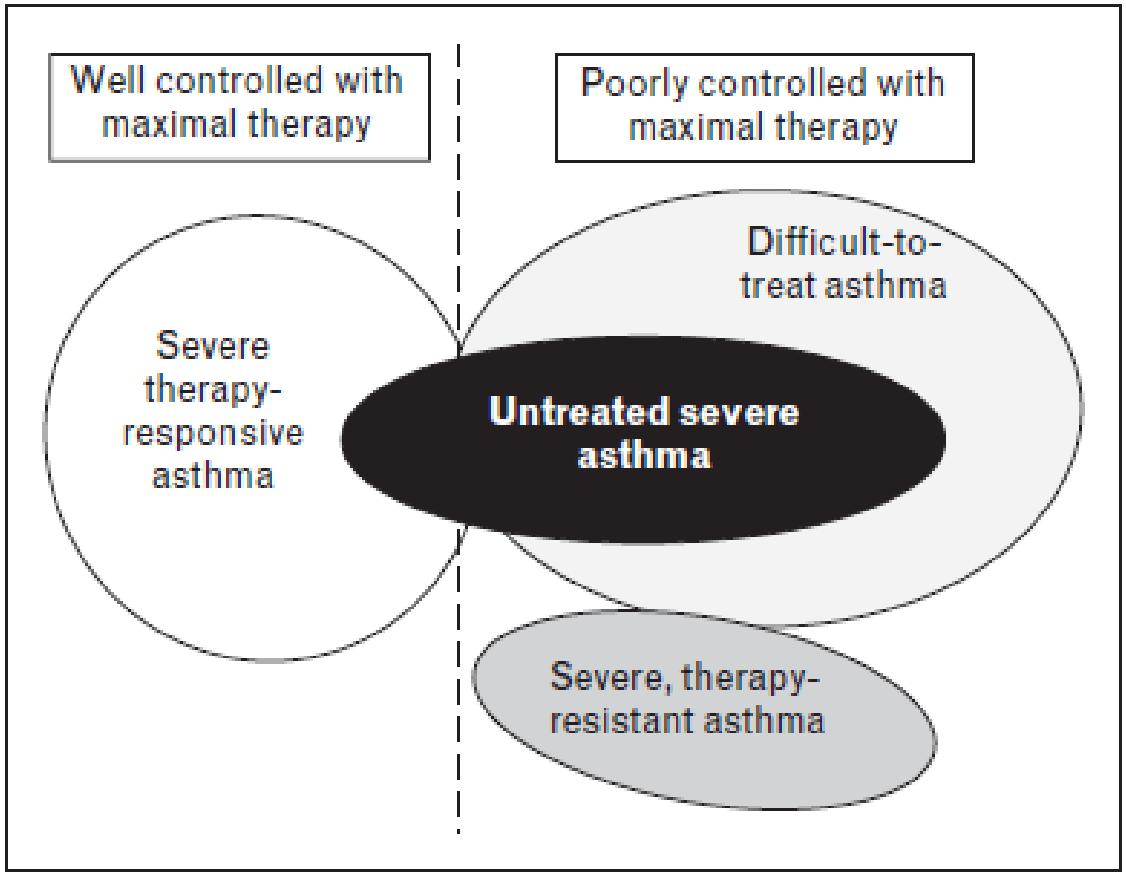


FIGURE 2. The WHO definition of severe asthma.

JACI 2010; 126:926-938

Cincinnati Children's
changing the outcome together

Definition of Uncontrolled Asthma

- At least one of the following:
  - 1) Poor symptom control:
    - ACQ consistently>1.5, ACT <20
  - 2) Frequent severe exacerbations:
    - 2 or more bursts of systemic CS in the previous year
  - 3) At least one hospitalization, ICU stay or mechanical ventilation in the previous year
  - 4) Airflow limitation (reduced FEV1, FEV1/FVC)
  - 5) Asthma that worsens on tapering medications
    - High dose ICS, oral steroid, biologic

Cincinnati Children's
changing the outcome together

Terminology

- Uncontrolled asthma
  - Frequent symptoms and/or exacerbations
  - Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly
- Difficult-to-treat asthma
  - Asthma uncontrolled despite prescribing high dose controller treatment
  - Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities
- Severe asthma (a retrospective definition)
  - asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased *(Chung, ERJ 2014)*

  i.e. relatively refractory to corticosteroids (rarely completely refractory)

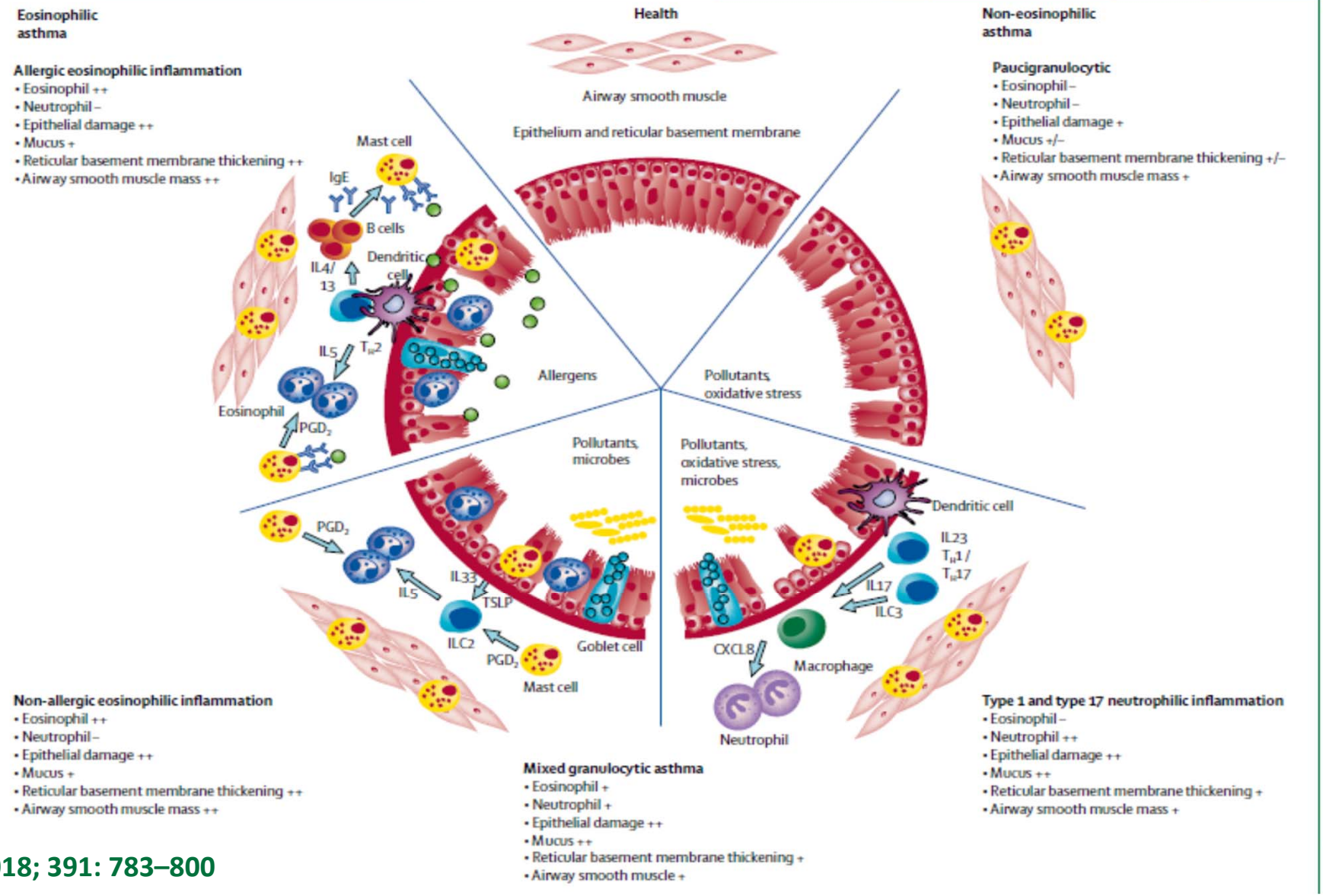
GINA April 2019

Cincinnati Children's
changing the outcome together

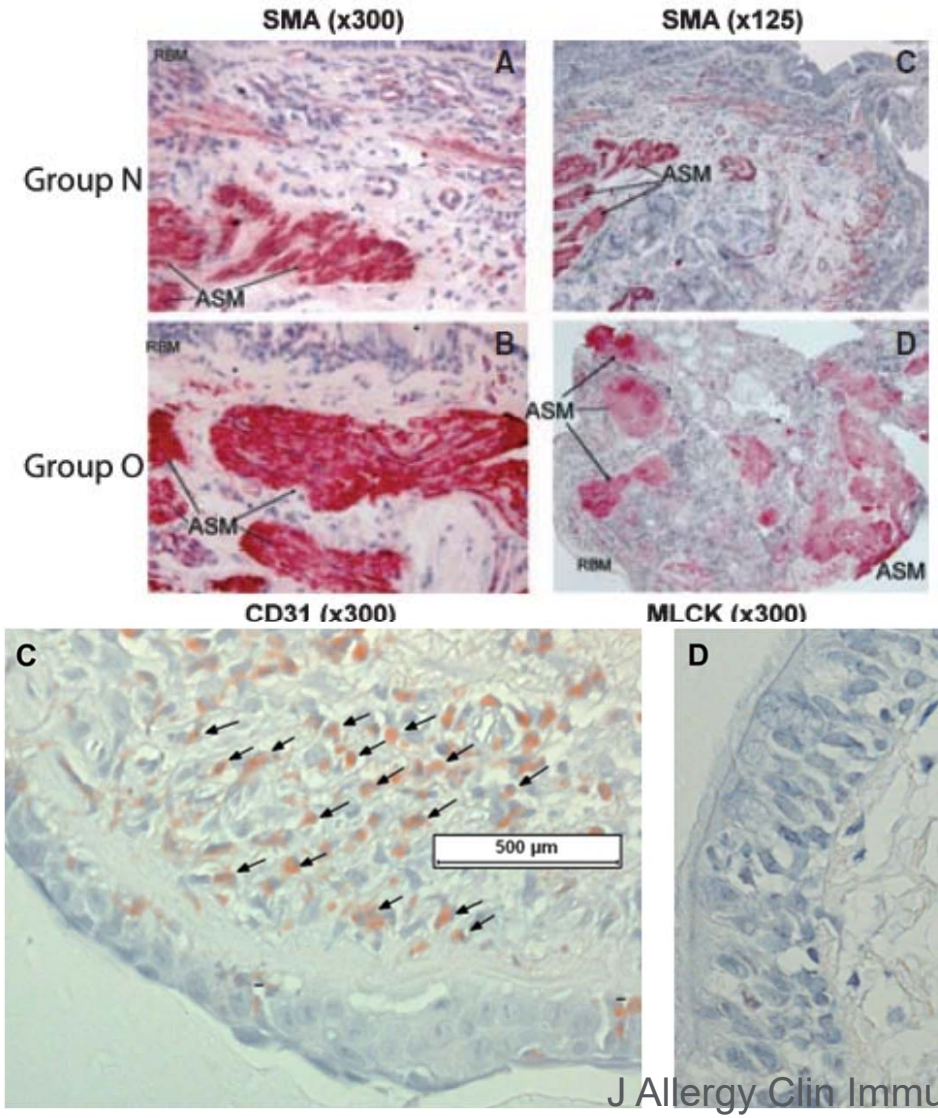
Pathobiology of Severe Asthma

- Structural airway alterations
  - greater airway smooth muscle mass
  - increased reticular basement membrane thickening
  - epithelial damage, angiogenesis
- Occurs with/without mucosal eosinophilia
- May develop with age and asthma duration

Cincinnati Children's
changing the outcome together



Lancet 2018; 391: 783–800



Allergy 2008: 63: 533–541

J Allergy Clin Immunol 2012;129:974-82.)

Cincinnati Children's
changing the outcome together

Severe Asthma: Inflammatory Pathways

- IL-4/IL-13 pathways (T2 high)
  - Allergen associated, eosinophilic, high IgE
  - Periostin and MMP7 increased
- IL-5/IL-33 pathways
  - Innate Lymphoid cells (ILC2)
  - Non-atopic, late onset disease
  - Exacerbations: eosinophilia, Cys-LT
  - Resistant to ICS, responsive to systemic steroids, anti-IL-5

Cincinnati Children's
changing the outcome together

Poon, AH, et al. Clin ex allergy 2012; 42:625-37

Severe Asthma: Pathways

- IL-17/IL-23 (T-2 low)
  - Sputum neutrophilia, variable airflow obstruction
  - Resistant to corticosteroids, responsive to macrolide antibiotics (?)
- Steroid Resistance
  - High IL-2, IL-4 reduces glucocorticoid binding affinity; elevated GRβ
- Others: PGD2, TSLP, IL-18, IFN-γ,

Cincinnati Children's
changing the outcome together

Characteristics of Severe Asthma

- High degree of atopy/allergic sensitization
- High IgE
- Eosinophilia (peripheral & sputum)
- Higher exhaled NO
- Lower lung function
  - Progressive loss of lung function
  - Air trapping
- Bronchodilator response
- Ethnicity/race

J Allergy Clin Immunol Pract. 2018 ; 6(2): 545–554
J Allergy Clin Immunol Pract 2017;5:901-8

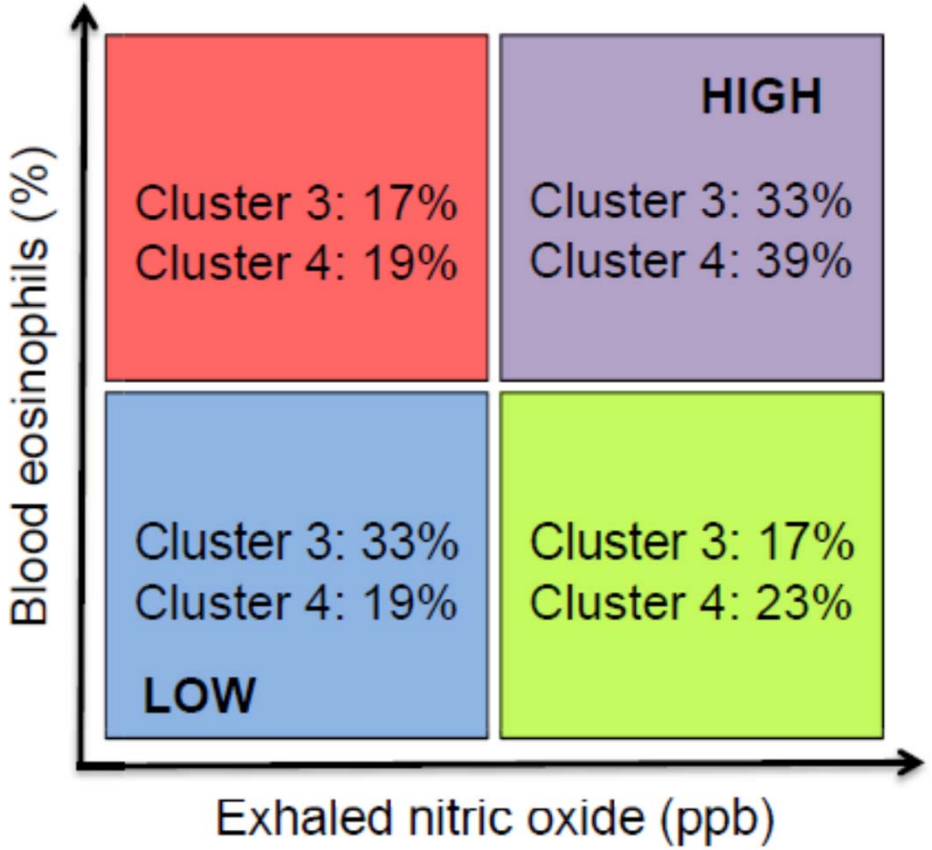
Cincinnati Children's
changing the outcome together

Heterogeneity of Severe Asthma

	Severe Cluster 3	Severe Cluster 4
Description	Co-morbid, difficult to treat	**Refractory asthma, low lung function**
Asthma Onset	Infancy	**Toddler to preschool**
Aeroallergen sensitization	High prevalence, multiple	High prevalence, multiple
Lung Function	Reversible obstruction	**Partially reversible**
Asthma medications	Multiple controllers, high dose ICS, **daily OCS**	Multiple controllers, high dose ICS
Utilization, past year	Multiple OCS bursts, acute visits, hospitalization	Multiple OCS bursts, acute visits, hospitalization
Co-morbidities	Sinusitis, GER, **obesity**	**Less frequent co-morbidities**

J Allergy Clin Immunol Pract 2017;5:901-8)

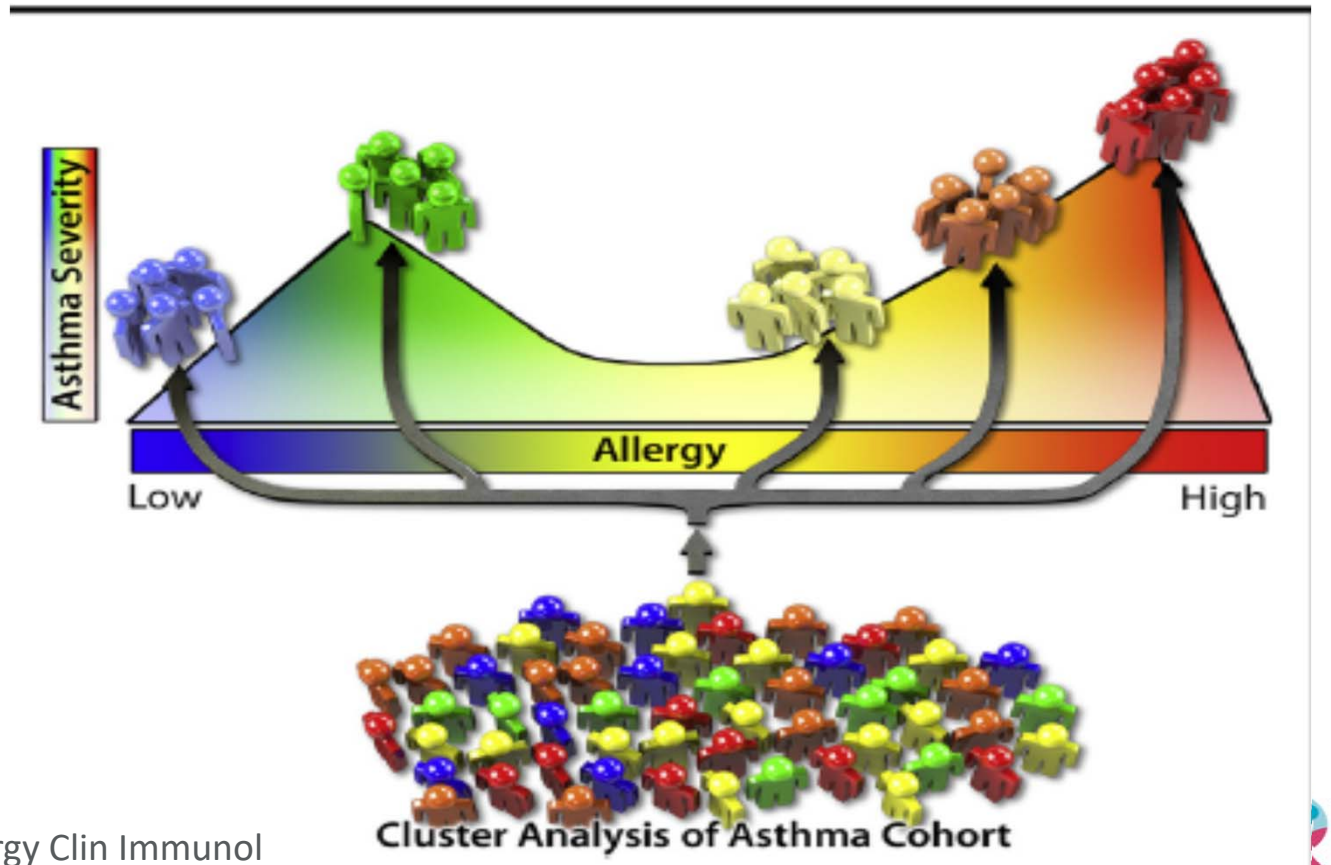
Biomarkers: Severe Childhood Asthma



J Allergy Clin Immunol Pract 2017;5:901-8)

Cincinnati Children's
changing the outcome together

Asthma Phenotypes/Clusters in Inner City Children



J Allergy Clin Immunol 2016;138:1016-29.)

Cincinnati Children's
changing the outcome together

Conditions That Mimic Severe Asthma

- Vocal cord dysfunction
- Central airways obstruction/compression
  - Congenital malformations
  - vascular ring
- Tracheobronchomalacia
- Recurrent (micro) aspiration, reflux, swallowing dysfunction
- Foreign body
- Primary ciliary dyskinesia
- Habit Cough
- Bronchiolitis obliterans
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immunodeficiency
- Connective tissue disease (EDS)
- Interstitial lung disease
- Congenital heart disease
- Carcinoid or other tumor
- Mediastinal mass, enlarged lymph nodes

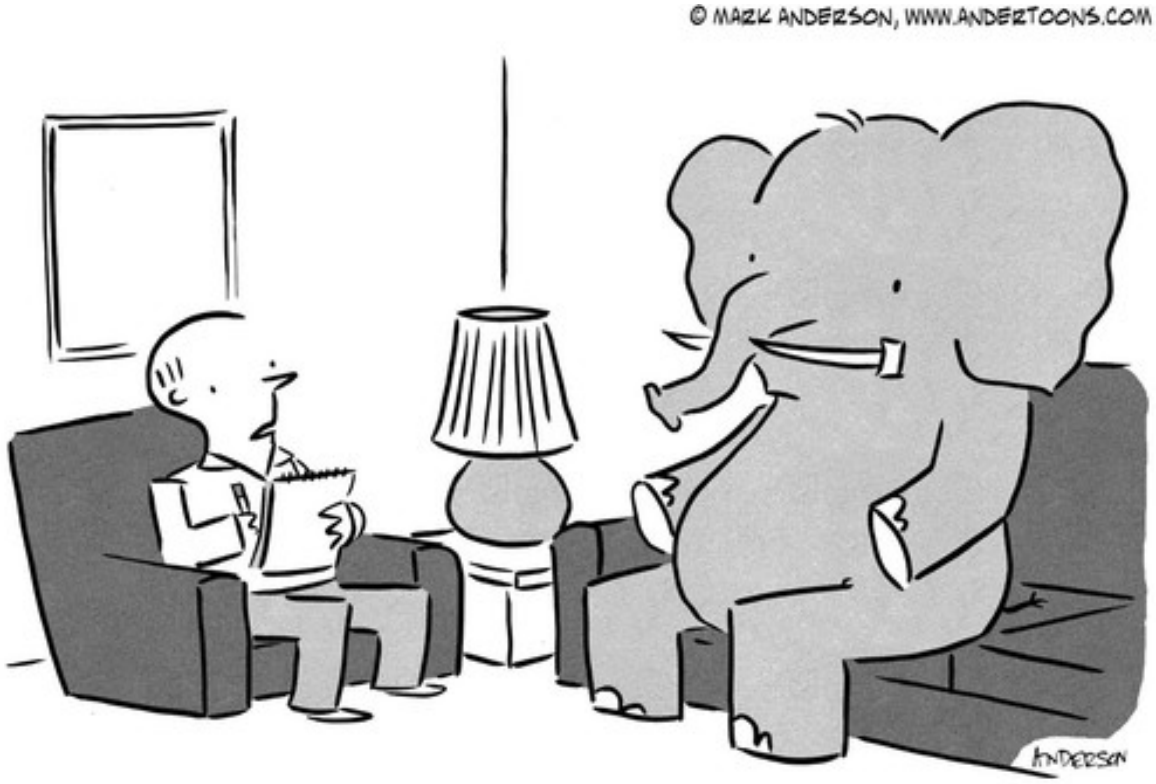
Cincinnati Children's
changing the outcome together

Co-morbid Conditions in Severe Asthma

- Reflux, aspiration
- Rhinosinusitis
- Poor adherence
- Ongoing allergen/irritant exposure
- Obesity
- Obstructive sleep apnea
- Bronchiectasis
- Eosinophilic syndromes
- Allergic bronchopulmonary aspergillosis
- Fungal sensitization asthma

Cincinnati Children's
changing the outcome together

ADHERENCE



"Let's try some role playing. I'll be the elephant in the room and you address me."

Cincinnati Children's
changing the outcome together

Question

- The proportion of patients who are non-adherent to prescribed doses of daily controller medications for asthma is approximately:
  - A) 10%
  - B) 20%
  - C) 50%
  - D) 80%

Cincinnati Children's
changing the outcome together

Correct Answer

- C: 50%

Cincinnati Children's
changing the outcome together

Adherence to Inhaled Steroids

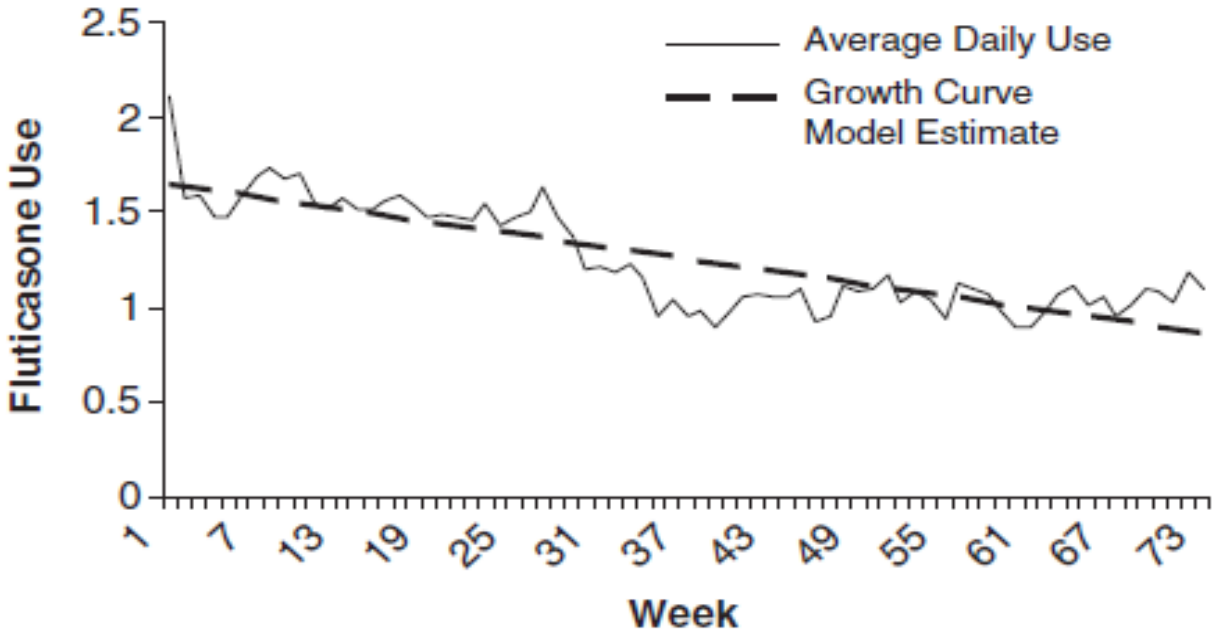


Figure 1. Individual growth curve for fluticasone use.

Rohan, et al. Journal of Pediatric Psychology 35(4) pp. 394–404, 2010

Cincinnati Children's
changing the outcome together

Severe Asthma Management

- Confirm the diagnosis: Is it asthma?
- Identify co-morbidities
- Address adherence and proper med use
- Environmental exposures
  - Unrecognized allergen and irritant exposure
- Psychobehavioral issues: child and parent
- Shared decision making

Cincinnati Children's
changing the outcome together

Treatment Options for Severe Asthma

- High Dose ICS+LABA*, LTRA*
- Tiotropium
- Oral corticosteroids?
- Biologics
  - Omalizumab, Mepolizumab, Benralizumab, Dupilumab, (Reslizumab)
- Others: macrolide antibiotics, allergen immunotherapy, bronchial thermoplasty

*LABA: long acting beta-agonist
LTRA: leukotriene receptor antagonist

Cincinnati Children's
changing the outcome together

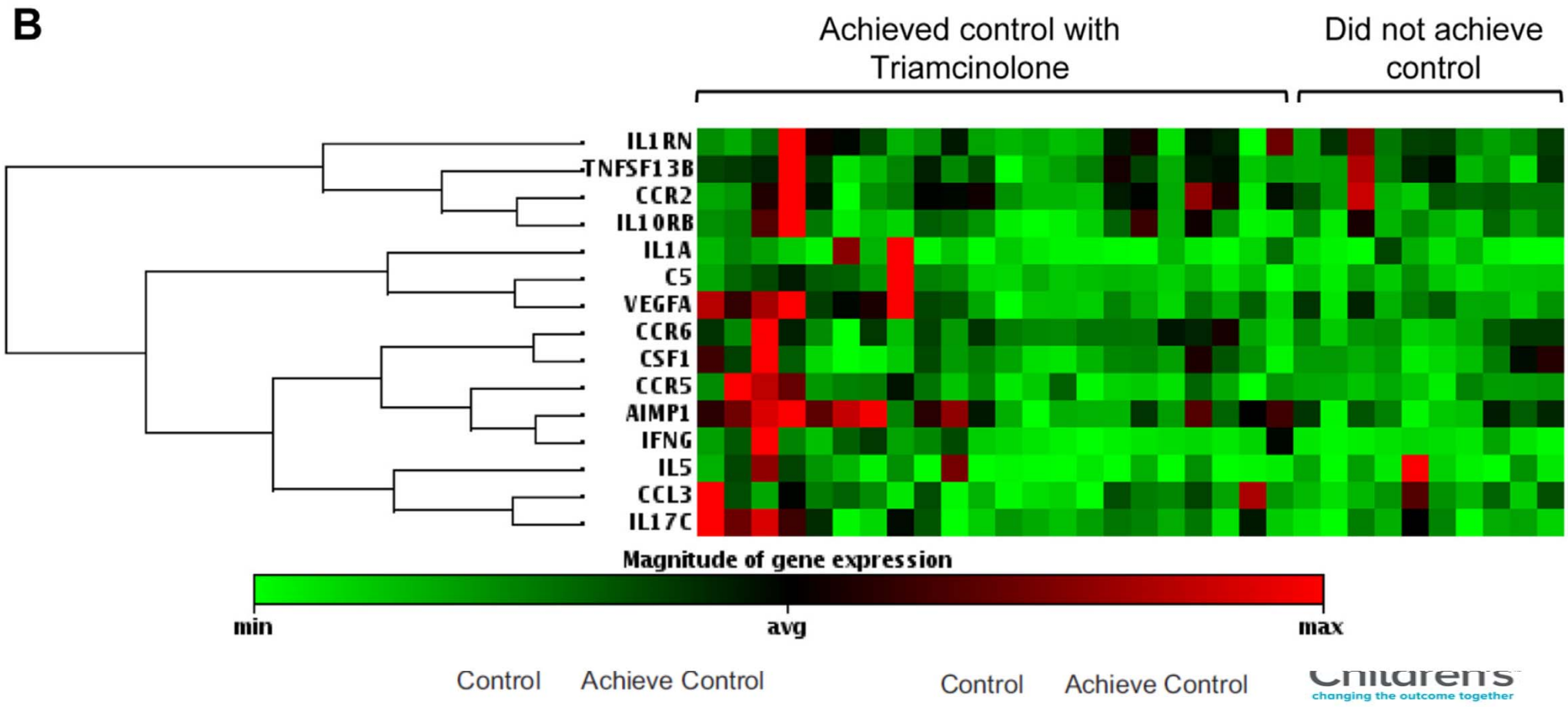
High Dose Corticosteroids

- Relative steroid resistance/insensitivity
  - 11% of children totally responsive (Sx, PFT, FeNO, BD response)
  - 43% obtained control with IM steroids
  - 30% of adults require oral steroids + ICS for control
- Associated with several co-morbidities
  - Obesity
  - Low vitamin D
  - Smoking
  - Persistent high allergen exposure
  - Low T2 phenotype

Eur Respir J 2009; 34: 1052–1059;
J Allergy Clin Immunol Pract 2017;5:410-9

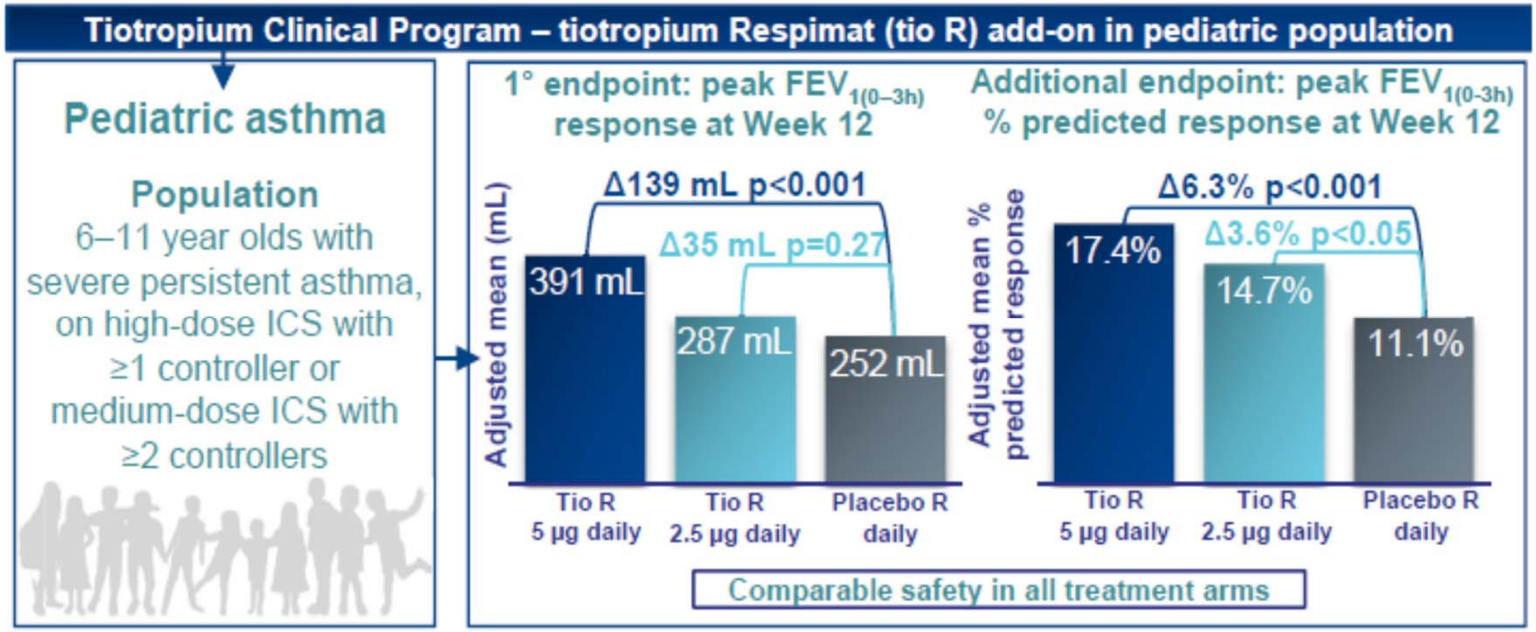
Cincinnati Children's
changing the outcome together

Heterogeneity of Steroid Response



J Allergy Clin Immunol Pract 2017;5:410-9

Tiotropium in Children age 6-11 yr

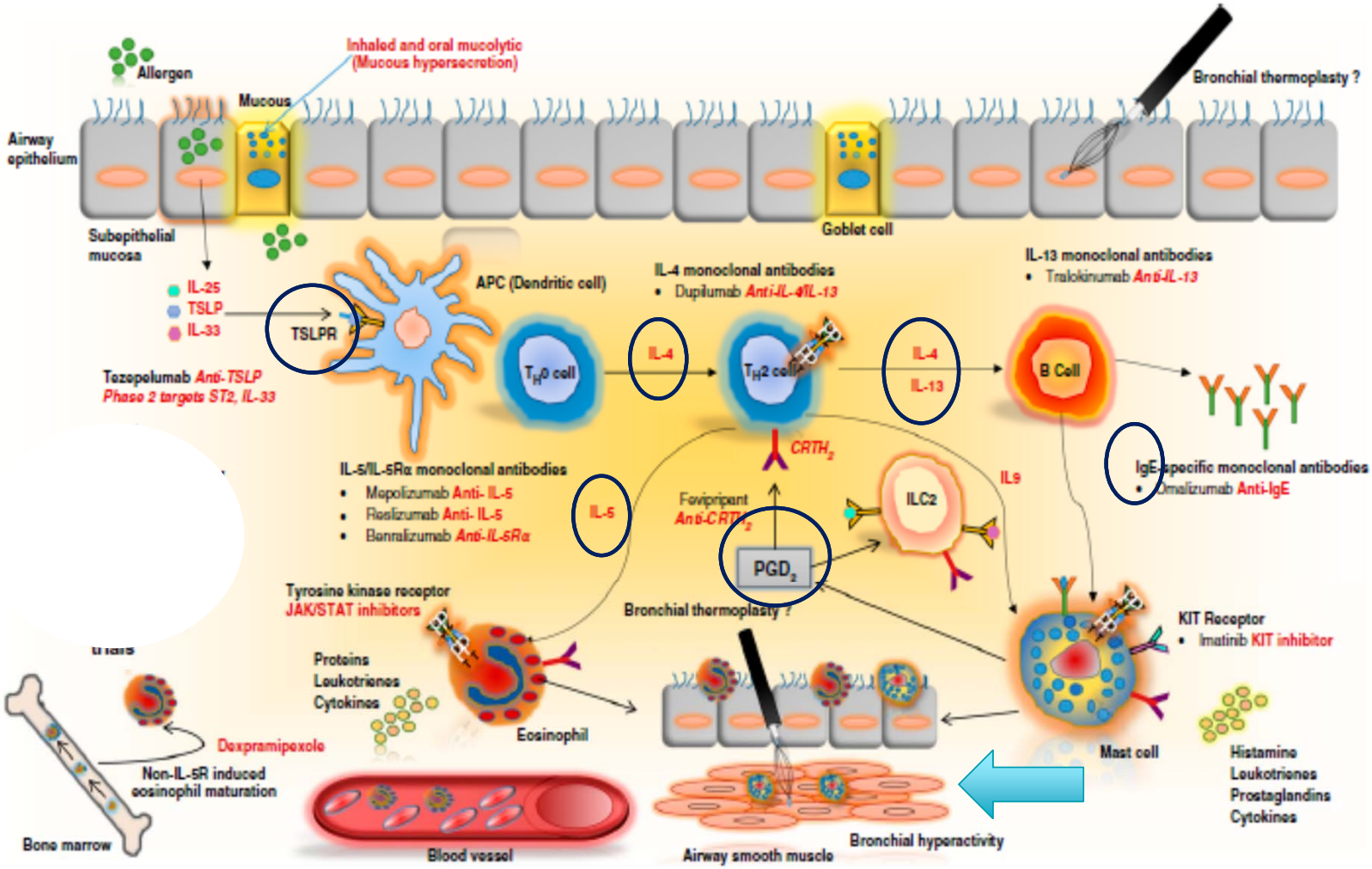


All groups had similar improvement in ACQ

Szefler S, et al. J Allergy Clin Immunol 2017; 40:1277-87

Cincinnati Children's
changing the outcome together

Asthma Treatment Targets



Am J Respir Crit Care Med Vol 199, 823–829:2019

Question

- A 12 yo boy with severe asthma is being considered for biologic therapy. His FEV1 is 98% predicted and his weight is 85 kg. His peripheral eosinophil count is 325 cells/ul, IgE is 1500 IU (normal 0-450 IU) and he is allergic to eggs only.

Cincinnati Children's
changing the outcome together

- Based on the data provided, which biologic is best suited for this patient?
  - A) Omalizumab
  - B) Reslizumab
  - C) Benralizumab
  - D) Tralokinumab

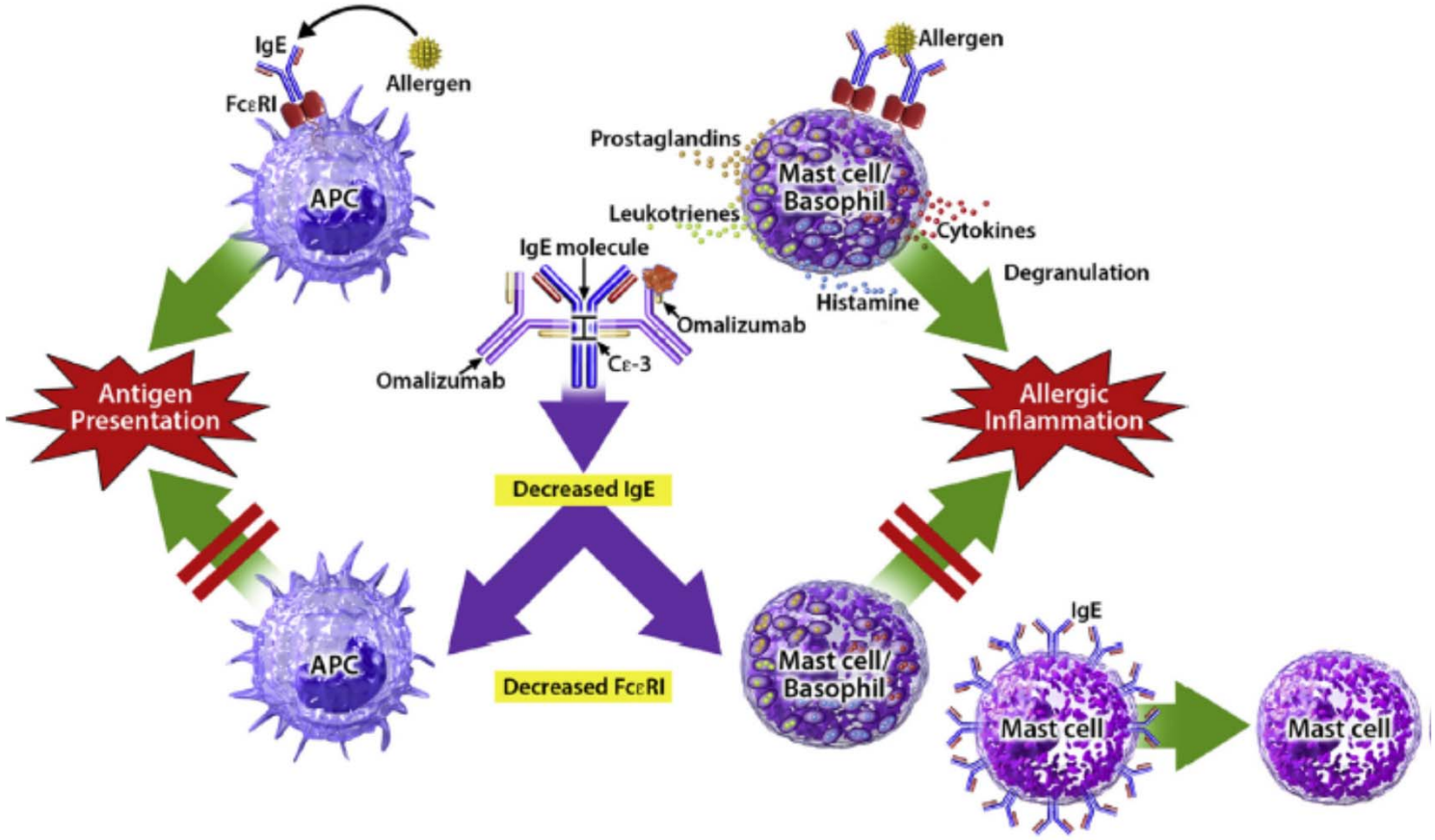
Cincinnati Children's
changing the outcome together

Correct Answer

- C: Benralizumab

Cincinnati Children's
changing the outcome together

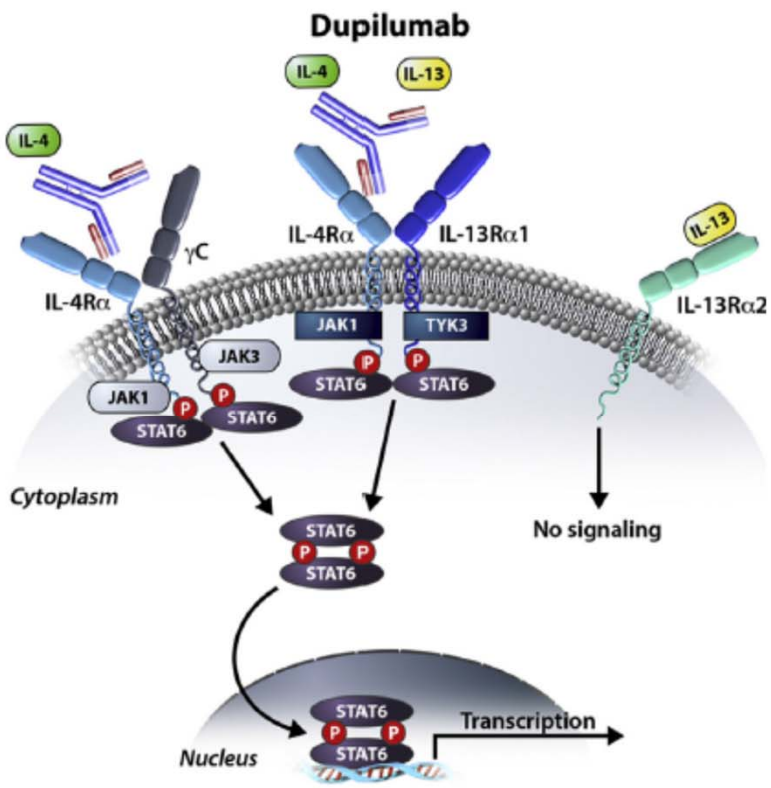
Targeting IgE

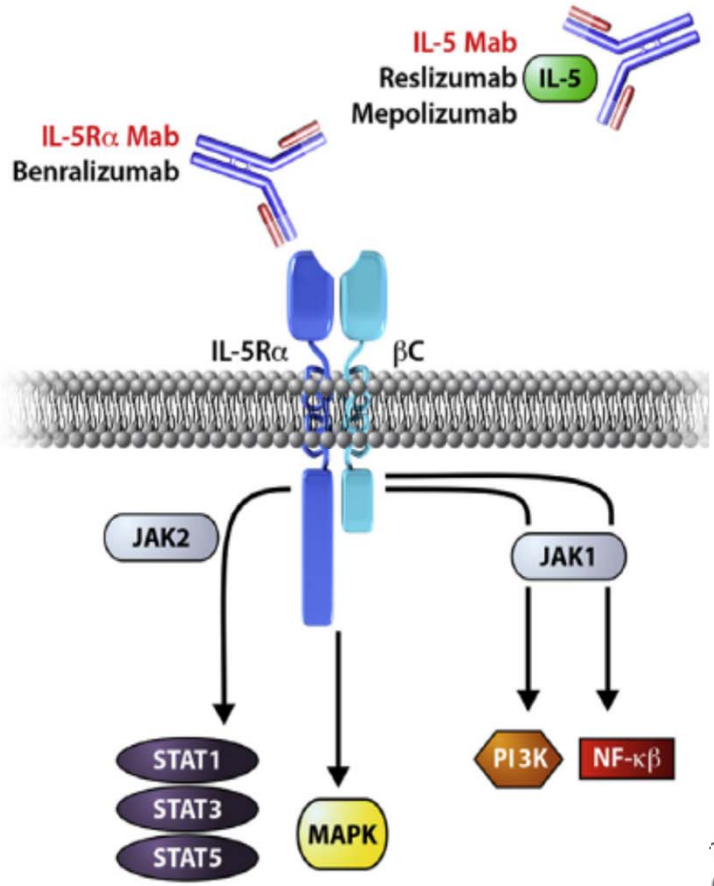


(J Allergy Clin Immunol 2017;139:1411-21

Cincinnati Children's
changing the outcome together

Targeting Cytokines





(J Allergy Clin Immunol 2017;139:1411-21

Biologic Therapy	Mechanism of Action	Exacerbation	Lung Function
Omalizumab (Xolair) > 6 years	Anti IgE; prevents IgE binding to receptor on mast cells	Reduces by ~25->60%	Minimal or equivocal improvement
Mepolizumab (Nucala) 6 yr +	Anti-IL5; prevents IL5 binding to receptor	Reduces by ~50%	Inconsistent effect
Benralizumab (Fasenra) 12 yr +	Anti-IL5 receptor; binds to IL5 receptor α; apoptosis of eos and basos	Reduces by 25-60%	Improves
Dupilumab (Dupixent) 12 yr +	Anti-IL4 receptor; blocks IL-4 and IL-13 signaling	Reduces by 50-70%	Improves

Biologic Therapy

- Omalizumab (anti-IgE)
  - sensitized to ≥ 1 perennial allergen
  - IgE 30- 1300 (1600) IU/ml (weight restrictions)
  - SC injection every 2-4 weeks
    - Black box warning for anaphylaxis
- Mepolizumab (anti IL-5)
  - 100 mg, SC every 4 weeks
  - Peripheral eos > 150/µl at screening or >300/µl in past 12 months
  - Anaphylaxis, zoster

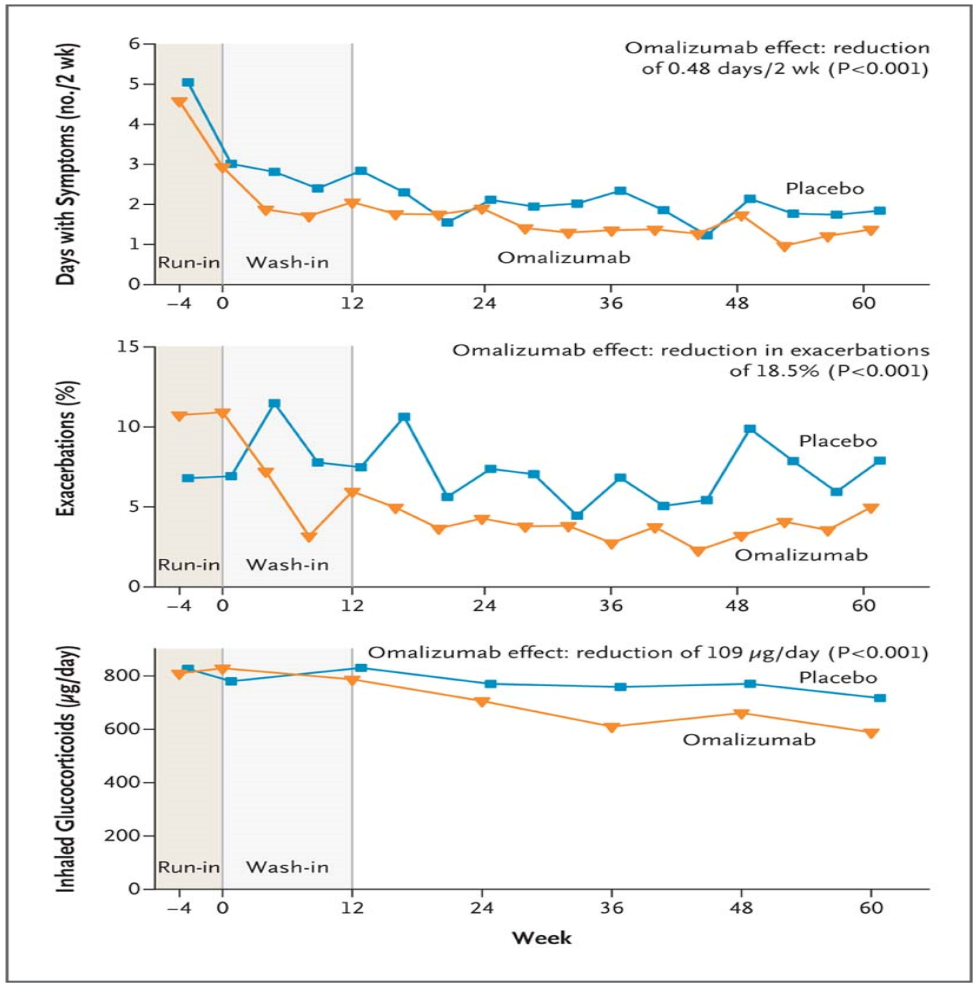
Cincinnati Children's
changing the outcome together

Biologic Therapy

- Benralizumab (anti IL-5 receptor)
  - 30 mg SC q 4 weeks x 3, then Q 8 weeks
  - No eos requirement but better effect with higher eos(>300), FeNO
- Dupilimab (anti-IL4/13)
  - 400(600) mg SC x 1 then 200(300) mg q 2 weeks
  - Better effect with higher eos (>300), FeNO
  - Home administration

Cincinnati Children's
changing the outcome together

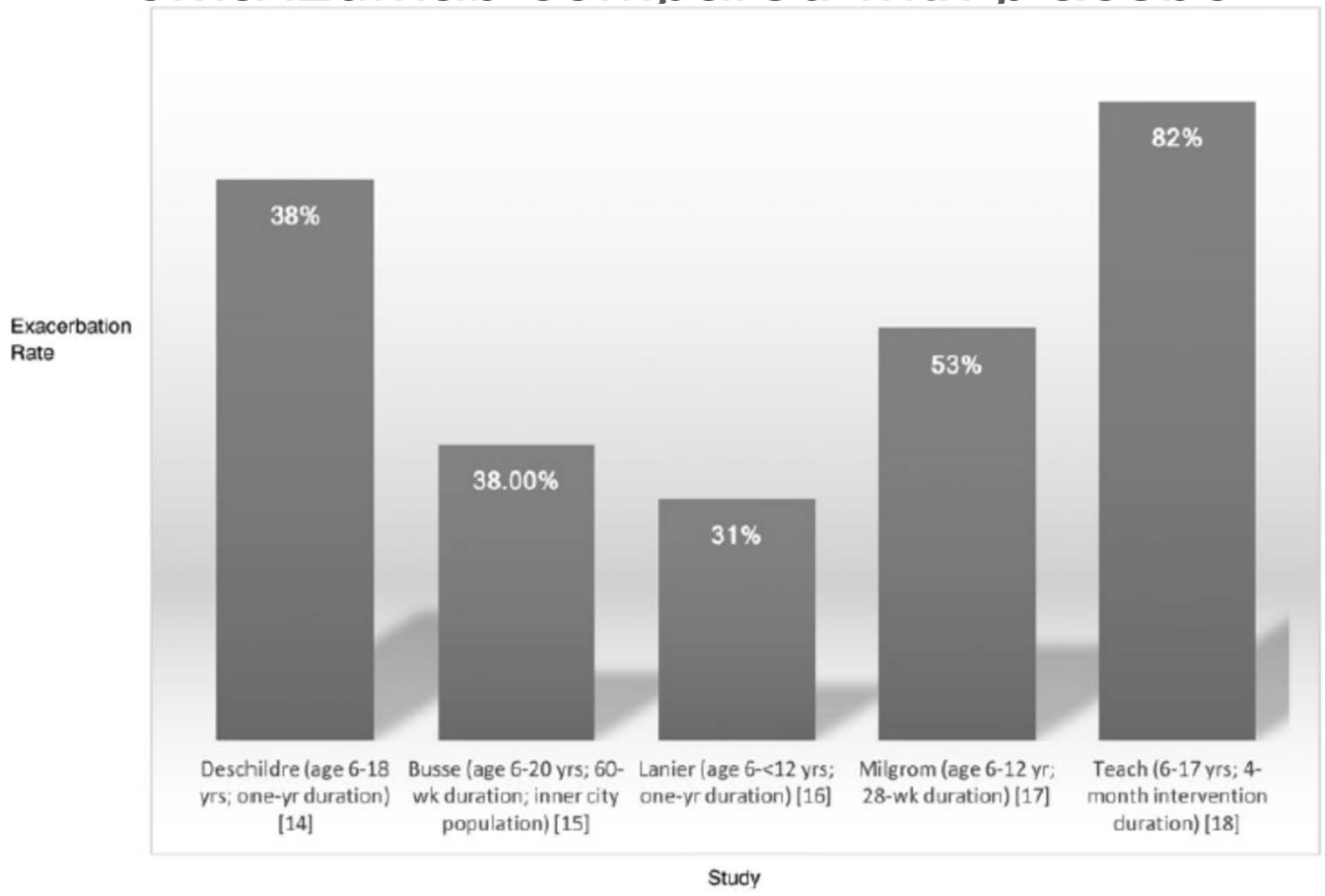
Omalizumab Effect on Asthma



N Engl J Med 2011;364:1005-1015

Cincinnati Children's
changing the outcome together

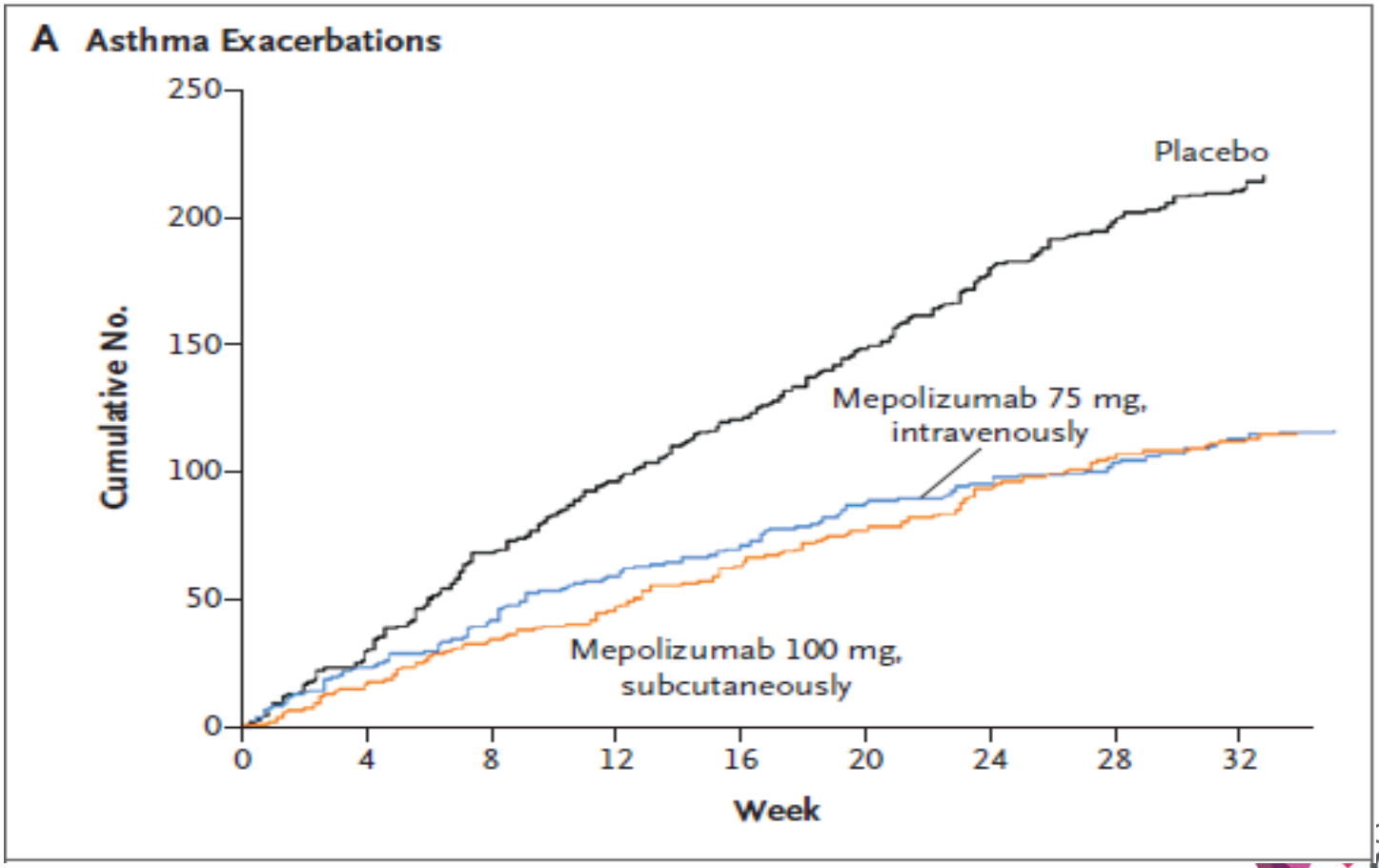
Decrease in exacerbation rate with omalizumab compared with placebo



Cincinnati Children's
changing the outcome together

Pediatr Aller, Immunol, Pulm Volume:31(3), 2018

Mepolizumab in Eosinophilic Asthma



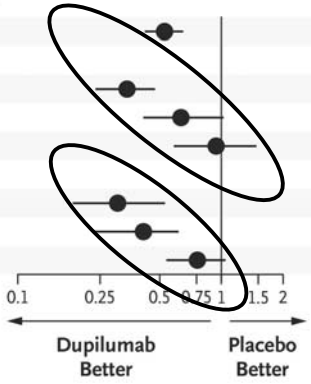
Cincinnati Children's
changing the outcome together

N Engl J Med 2014;371:1198-207.

Dupilumab: Risk of Severe Asthma Exacerbations According to Baseline Blood Eosinophil Count and Baseline FE_{NO}.

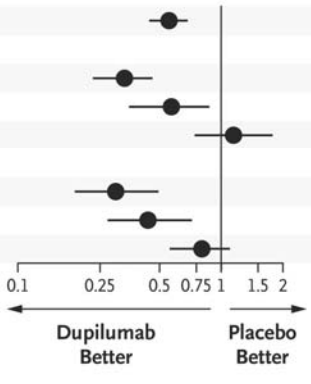
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

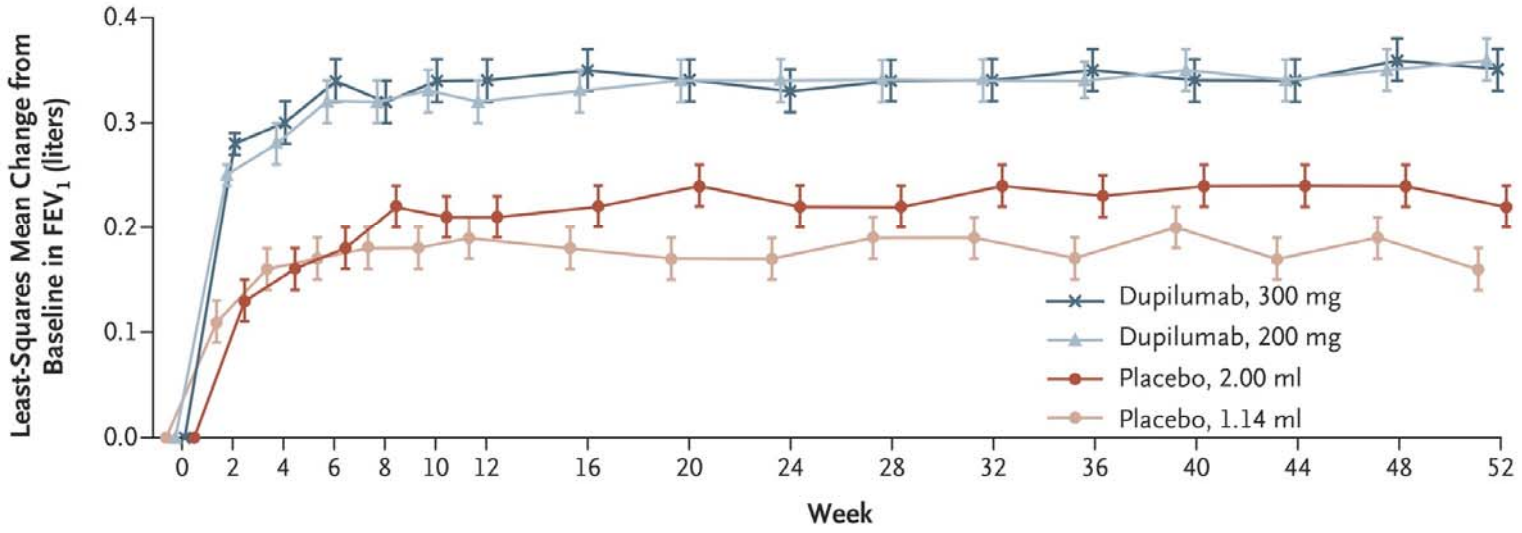
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Castro M et al. N Engl J Med 2018;378:2486-2496

The NEW ENGLAND JOURNAL of MEDICINE

Dupilumab: Change FEV_1 from Baseline over the 52-Week Intervention



No. at Risk																	
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Castro M et al. N Engl J Med 2018;378:2486-2496

The NEW ENGLAND JOURNAL of MEDICINE

Currently Approved Biologics

Therapy	Ex	Lu	of Acti	Dosing and Route
Omalizumab	Redu			0.016 mg/kg per IU of IgE y 2–4 375 mg in States; 150–600 ng in European Union)*
Mepolizumab				mg s.c. every 4 wk
Res				Weight-based dosing of mg/kg i.v. every 4 wk
Benralizumab			s to IL-5 recepto causes apoptosis of eosinophils and basophils	30 mg s.c. every 4 wk for three doses; followed by every 8 wk subsequently
Dupilumab	Re	oved	Anti–IL-4R; binds to IL-4 receptor α; blocks signaling of IL-4 and IL-13	200 or 300 mg s.c. every 2 wk

Cost per year: ~$36,000

Am J Respir Crit Care Med Vol 199:433–445, 2019

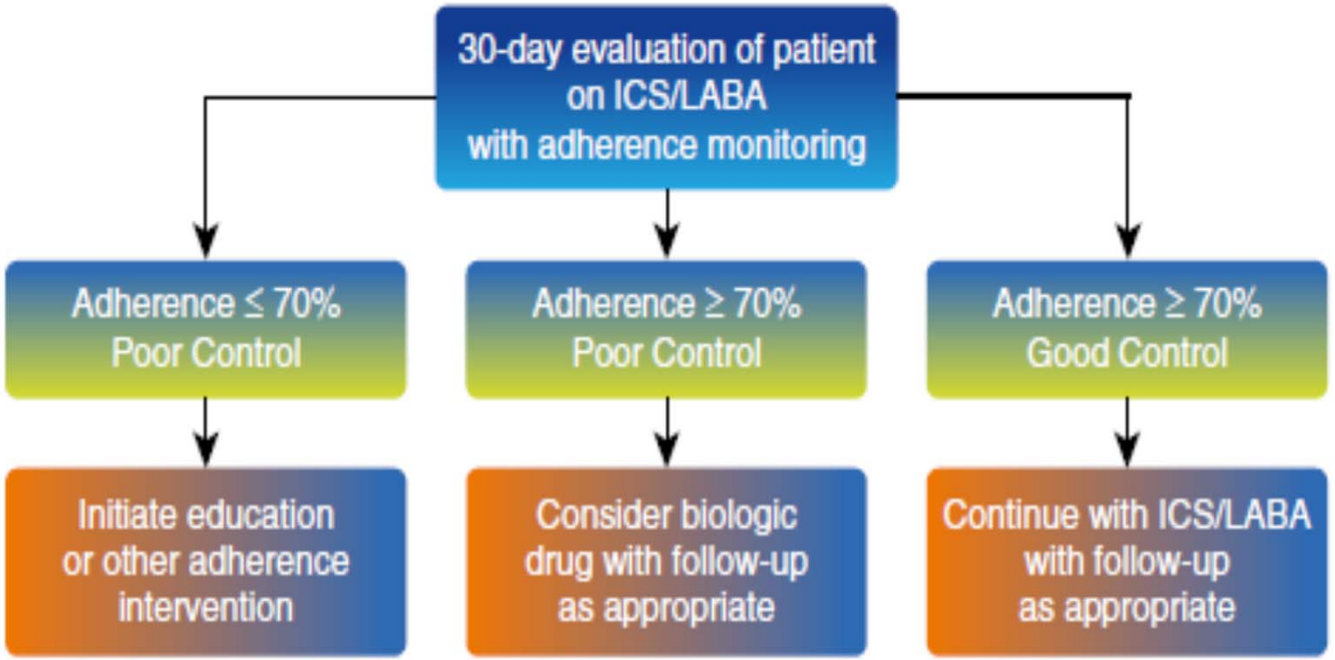
nati
dren's
e outcome together

Defining Response to Biologic Therapy

- Adequate response defined as:
  - at least 50% fewer asthma exacerbations needing systemic corticosteroids in those with >4 exacerbations in the previous 12 months or
  - clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control

Cincinnati Children's
changing the outcome together

Adherence Assessment in Biologic Therapy Decisions



Bender B. AJRCCM,Volume 199 (4):400-02; 2019

Cincinnati Children's
changing the outcome together

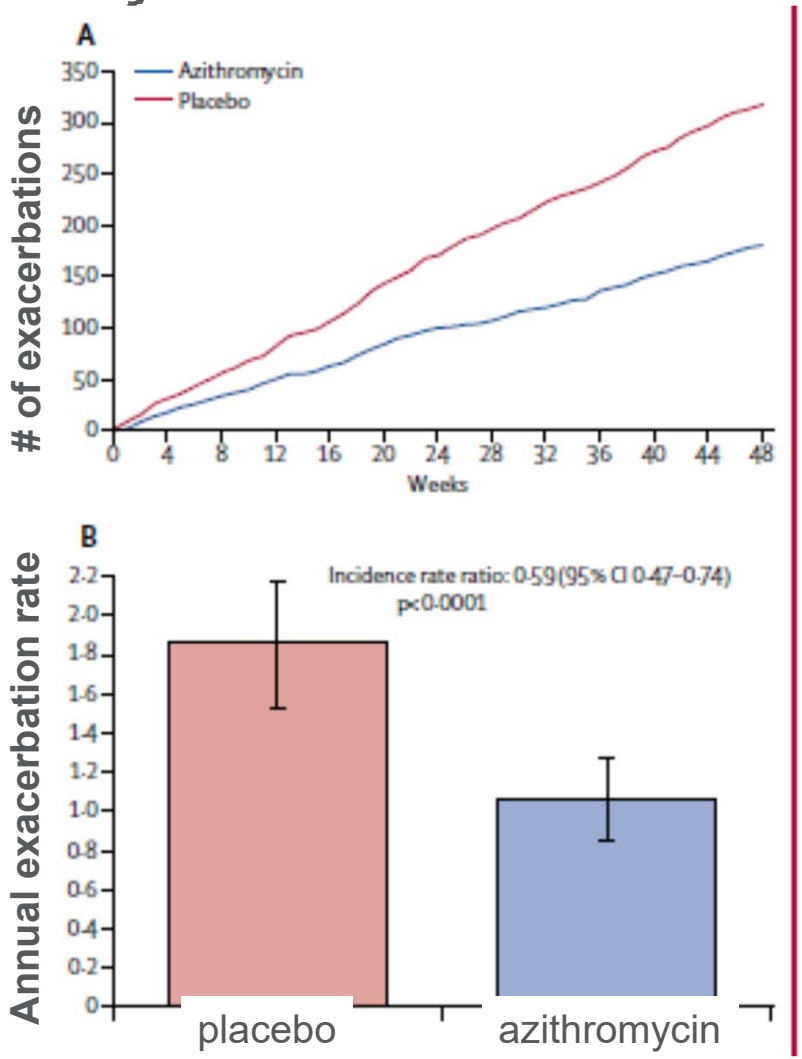
Macrolide Antibiotics

- Effective in other chronic respiratory disorders
- Anti-inflammatory effects on
  - PMN
  - Macrophages
  - Epithelium
  - Lymphocytes
- Antibacterial and anti-viral actions
- Possible effectiveness in certain phenotypes
- Cardiovascular risk

Lancet Respir Med 2014 2: 657–70

Cincinnati Children's
changing the outcome together

Azithromycin in Moderate-Severe Asthma



***Lancet* 2017; 390: 659–68**

Cincinnati Children's
changing the outcome together

Other Potential Treatments

- Bronchial thermoplasty
  - possible trial in adolescents
- **In Clinical trials:anti-PGD2, TSLP, probiotics**
- Anti-fungal agents
  - Adjunct treatment for ABPA
  - fungal sensitization asthma; not recommended
- Theophylline
  - anti-inflammatory; Improves steroid sensitivity
- Allergen immunotherapy
  - Not safe/recommended in poorly controlled asthma

Cincinnati Children's
changing the outcome together

Summary

- Is it asthma?
- Is it severe?
  - therapy resistant or difficult to treat?
  - Severe co-morbidities or severe asthma?
- Identify and manage co-morbidities
  - Allergy, obesity, OSA, GER, VCD
- Assign a phenotype/endotype
  - Phenotype specific treatment
- Non-medical interventions: adherence

Cincinnati Children's
changing the outcome together