Asthma and its phenotypes

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Phenotypic evaluation of asthma

- Asthma heterogeneous disease
  - Dx of asthma requires symptoms and reversible airway obstruction--many diseases meet
  - Classification of phenotypes limited
  - Previous classifications included allergic/extrinsic, non-allergic/intrinsic, aspirin sensitive, brittle
- Phenotype: “Characteristics of an organism resulting from the interaction of its genetic make-up and environment”
- Defining phenotypes should enhance understanding of pathobiology and ability to *target* therpy with biologics, etc

Potential breakdown of phenotypes

- Based on
  - Clinical aspects
  - Inflammation
  - Associated factors/triggers
- Can we begin to address overlap through integrated approaches to better target therapy?

I. Clinical Phenotypes

- Mild to severe
  - Easily controlled (mild) vs not easily controlled (severe)
- Not easily controlled/severe disease
  - Variable disease with frequent and/or severe exacerbations
  - Stable or progressive, but more marked airflow limitation

Severity

- Most broadly used classification of asthma
  - but is severity truly a phenotype?
- “Severity” based on level of symptoms, FEV1 and medication needs to maintain “control”
  - Very little longitudinal data suggest asthma progresses from mild to severe disease
    - Generally starts at some level of severity and stays there OR
    - “Second hit” moves patient from mild to more severe
  - No specific biomarkers identified for each level

“Not severe” asthma

- Asthma that achieves arbitrary level of control on currently available medications
- Likely majority of asthmatics
- “May” be more likely to have onset in childhood and allergic component

Severe asthma: Easiest to identify phenotypes

- Asthmatics who do not achieve specified level of control despite gold standard therapy and adequate control of co-morbidities
- Two broad clinical categories
  - Exacerbating severe asthma
  - Progressive/stable but marked airflow limitation
  - Each meet ATS workshop criteria for severe asthma
  - May be subgroups of “severe disease” that either don’t have asthma at all, or have “more” than just asthma…i.e., bronchiectasis

Frequent/severe exacerbaters vs stable/progressive obstruction

- Exacerbations (frequent and/or severe) and obstruction recognized as two “risk domains”
- Don’t always occur in same subjects, but when do, likely contributes to even greater severity
- Associated with differences in:
  - Physiology
  - Pathology
  - Prognosis
  - Profound differences in AQLQ

Severe asthma patients have high HCU despite standard care

Health Care Utilization	MILD	MODERATE	SEVERE
ER Ever	58%	66%	86%
ER past year	10%	20%	43%
Hosp Ever	28%	33%	74%
Hosp past year	<1%	6%	27%
ICU Ever	6%	9%	41%
Mechanical Vent	4%	6%	23%

SARP

Moore, JACI 2007

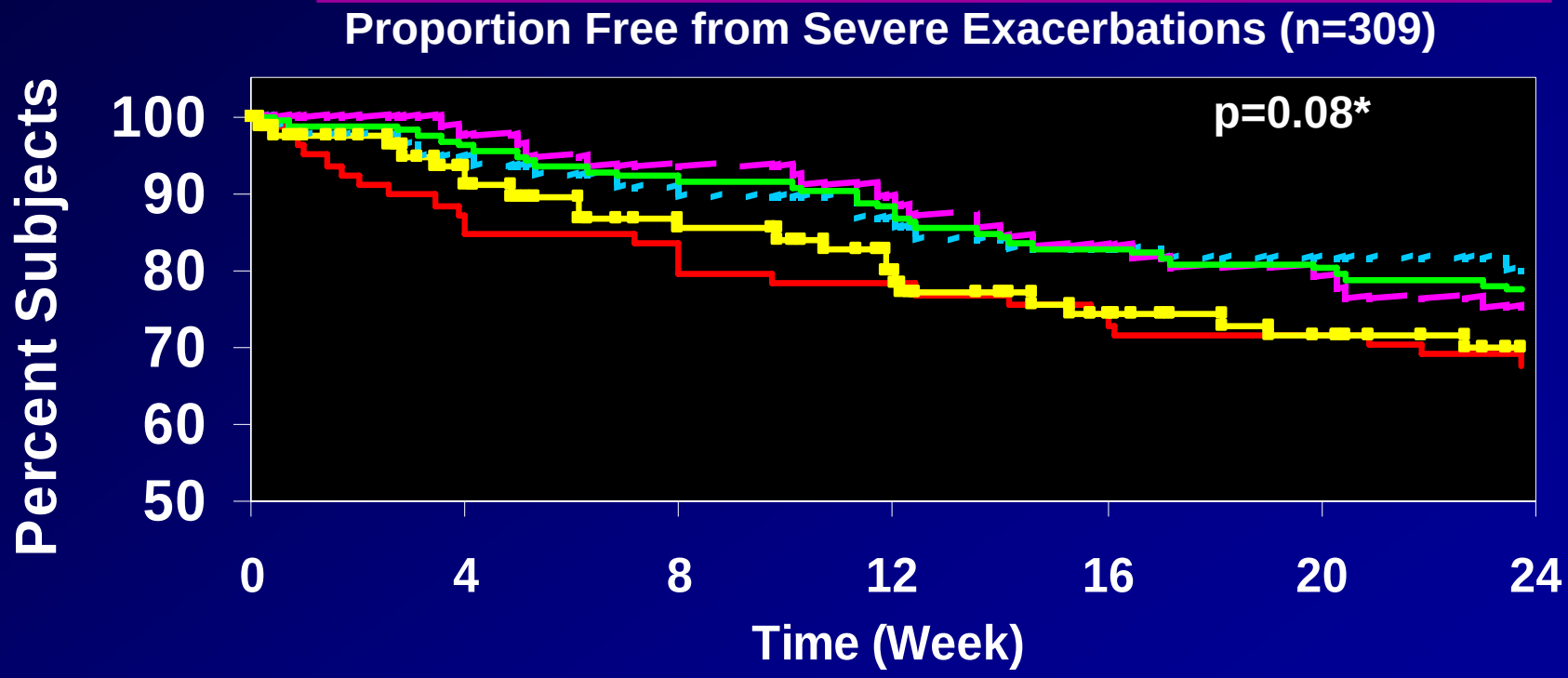
In fact, over 75% of all severe (SARP) asthmatics have EITHER history of ICU stay (ever), ER visit/hospitalization OR more than 3 oral steroid bursts in previous year

Severe exacerbaters more likely to:

- Be more reactive
  - PC20 and BD responsiveness
- Have
  - more sputum eosinophils
  - more steroid side effects
  - marginally lower FEV1
  - definable triggers: sinus, GERD
  - earlier age at onset
- Have no differences in:
  - IgE or allergy skin testing

SARP, Unpublished

Anti-TNF-α in severe asthma: Clearly a need to phenotype

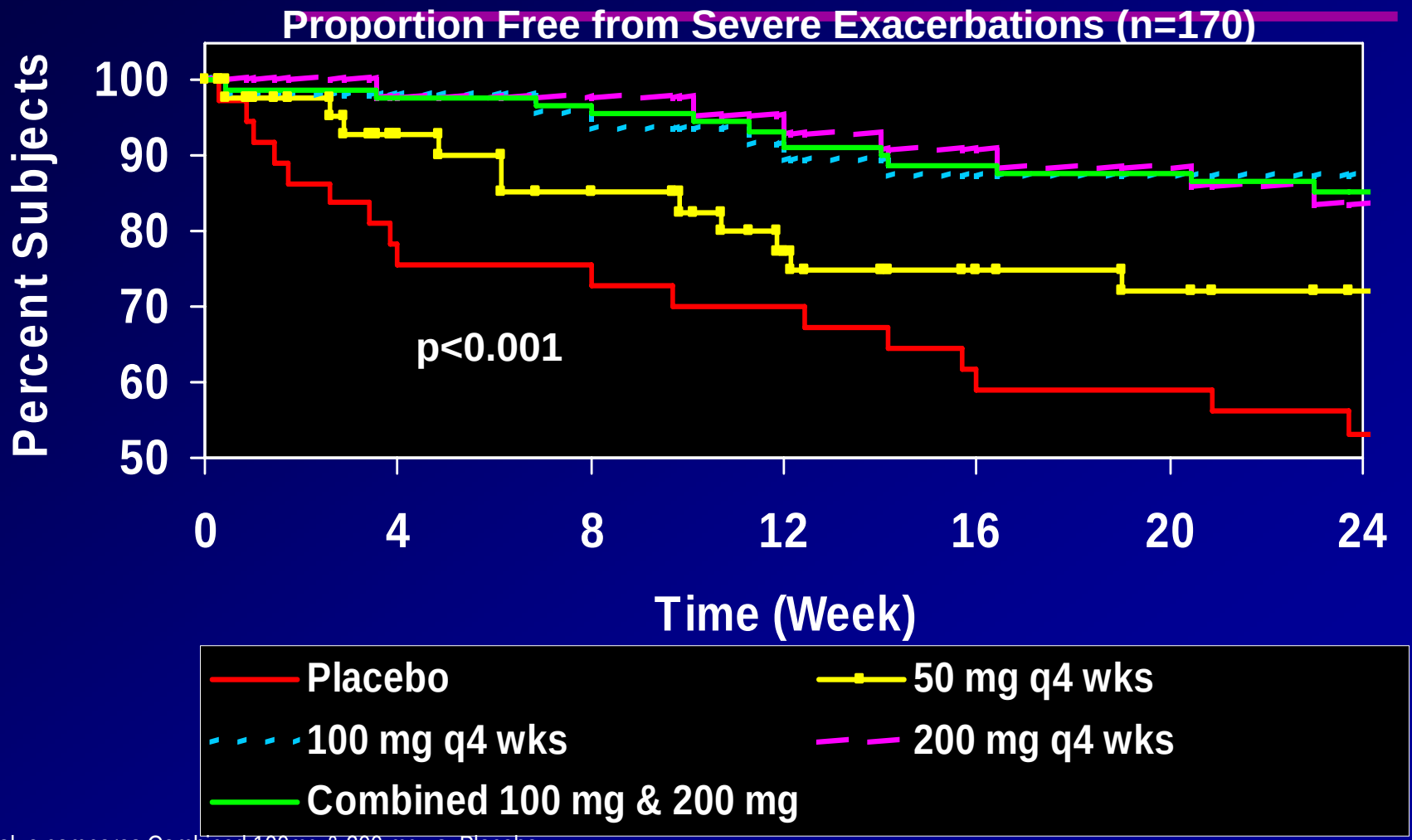


*P-value compares Combined 100mg & 200 mg vs. Placebo

Reversibility: A key element of severe asthma exacerbating subset

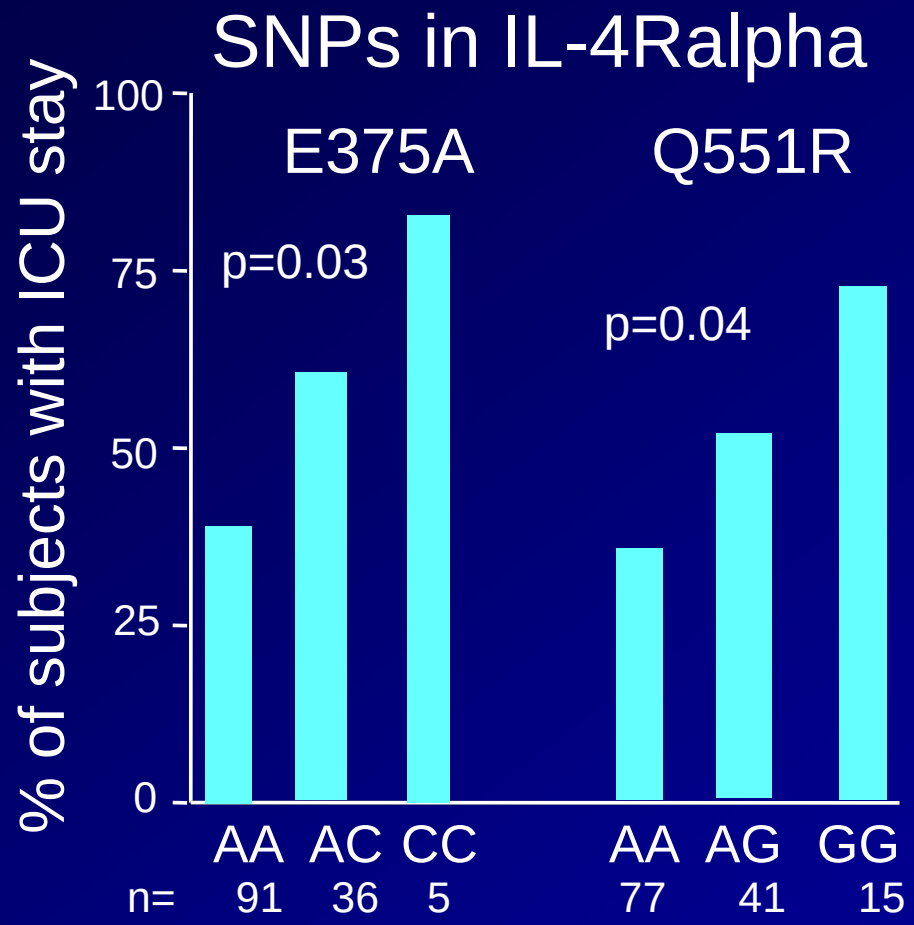
	Reversibility < 12% (n=144) Mean +/- SD	Reversibility ≥ 12% (n=164) Mean +/- SD
Baseline % predicted FEV_1	63.4 +/- 10.5	56.8 +/- 11.3
Baseline reversibility	5.5 +/- 5.0	26.1 +/- 14.2

Late onset, reversible with sinus hx much more likely to respond



P-value compares Combined 100mg & 200 mg vs. Placebo

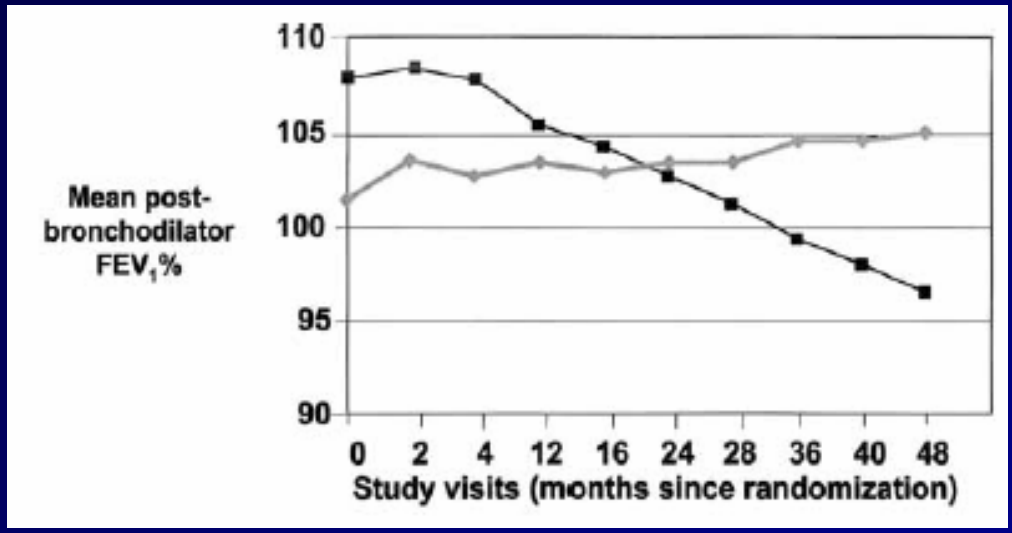
Genotypes also impact exacerbation “phenotype”



- Less frequent allele (in CA) associated with severe exacerbations
- Replicated in larger SARP cohort
- Significant with African Americans removed
- Similar differences in FEV1 by genotype

Wenzel S, Myers D, et al AJRCCM 2007

Declining FEV1 occurs in subset of asthma



Covar AJRCCM 2004

- Previously published data (CAMP trial, NEJM 2002) did not suggest overall decline in FEV1 in any of 3 Rx groups
- However, subset analysis suggested decline in FEV1 in a subset, which was NOT impacted by treatment with ICS

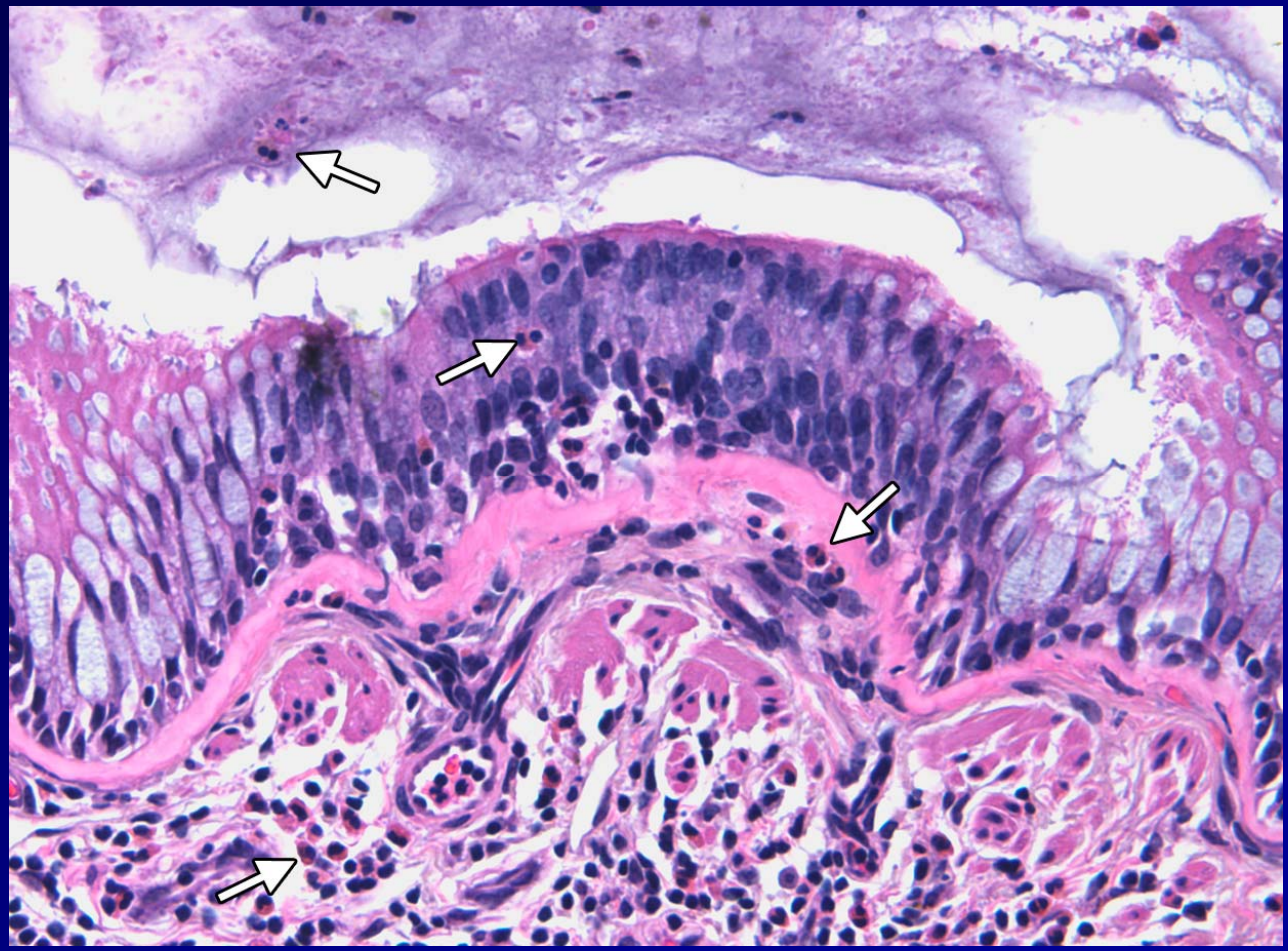
Being male and less allergic increased risk for decline in FEV1

Risk Factor	FEV1 ↓	No ↓ FEV1	p-value
Age	7.6±2	8.4±2	0.0001
Male sex	70%	57%	0.0003
Age at dx	3.4±2	4.1±3	0.0004
Atopy	77%	87%	0.0004
Serum IgE	928	1281	0.05

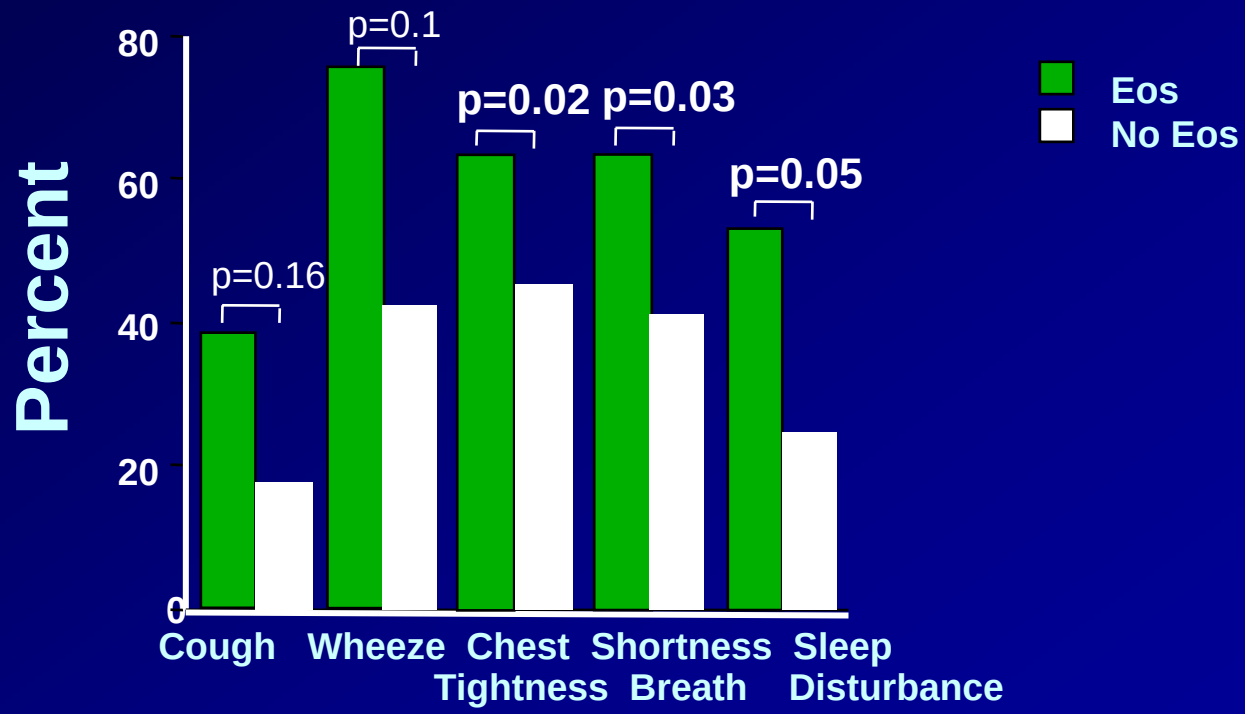
II. Inflammatory Phenotypes

- Eosinophilic
  - More common exacerbating phenotype
  - Strong evidence links symptoms, exacerbations and response to therapy
  - Less relation to atopy
- Non-eosinophilic
  - More likely to be obese
  - Relationship to smoking
  - May exacerbate less due to *asthma* and more due to co-morbidities
  - Neutrophilic inflammation may relate to lower FEV1

Eosinophilic inflammation: The ultimate exacerbation (death)



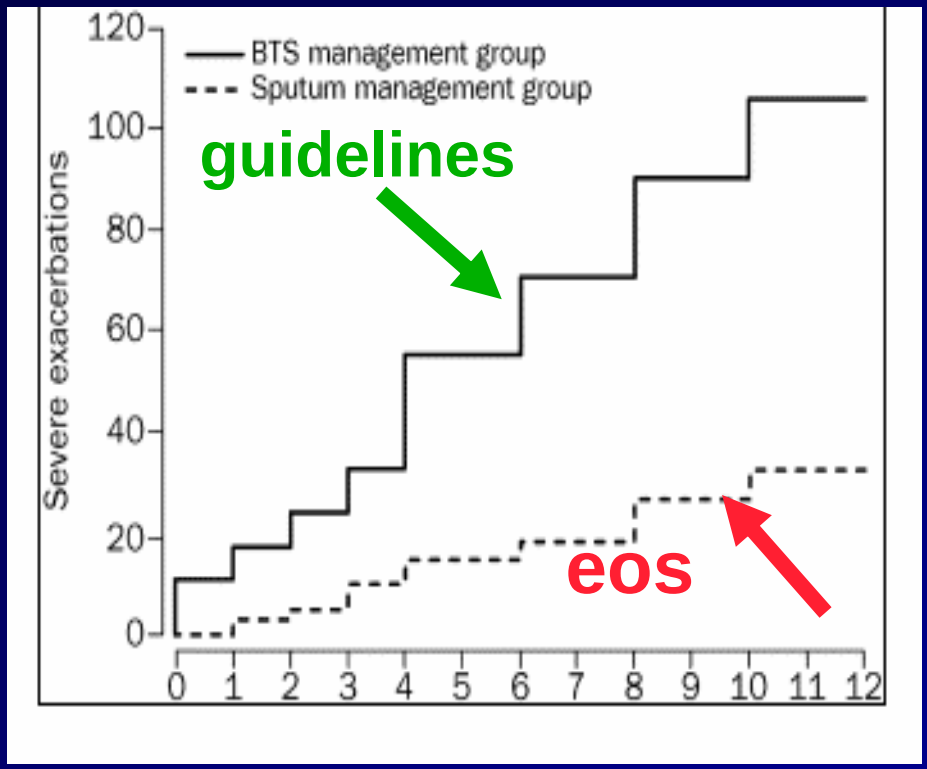
Persistent eosinophils: greater symptoms/severe exacerbations



***Symptoms "most or all of the time"**

Miranda,JACI, 2004

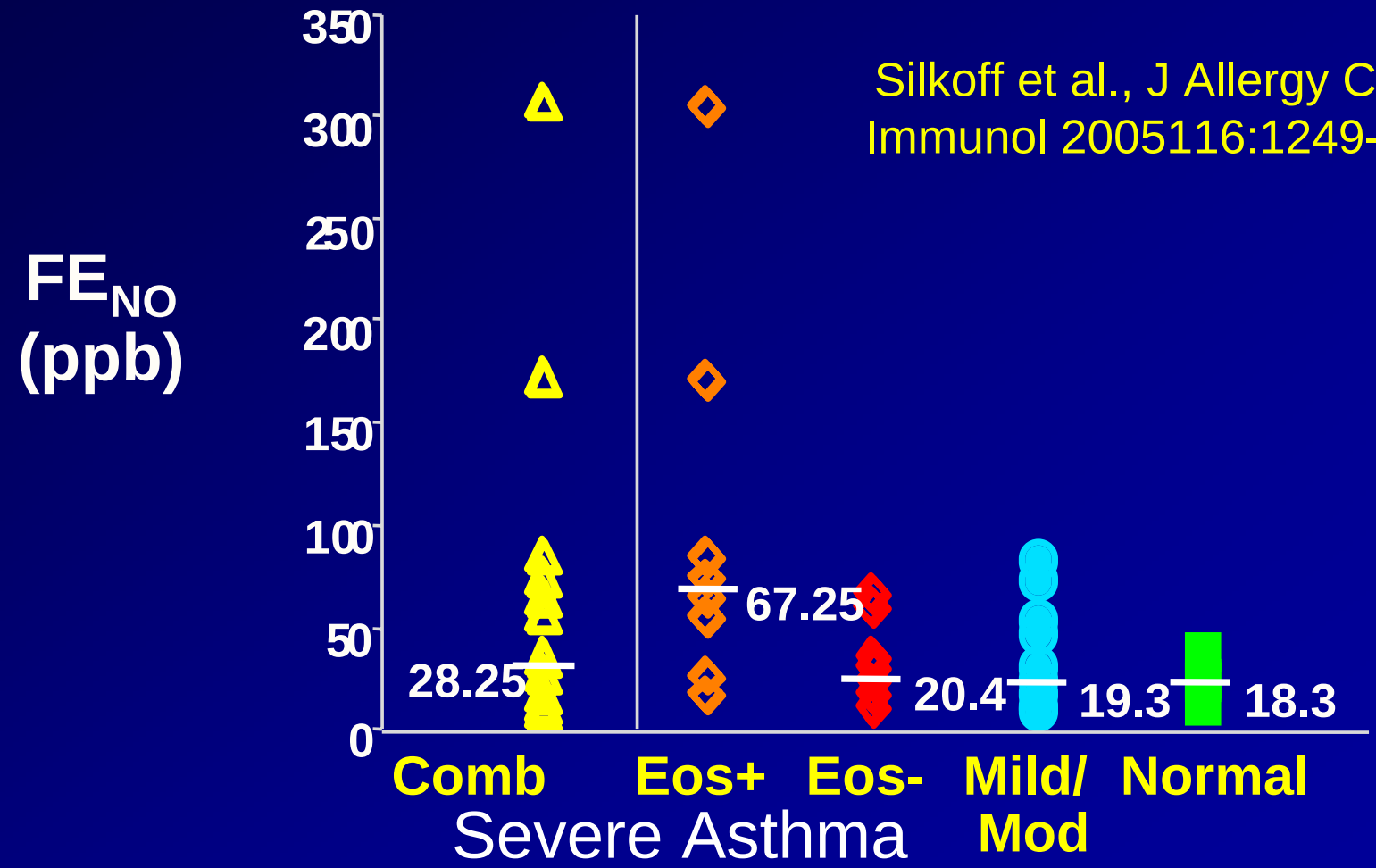
Controlling eosinophilic inflammation decreases exacerbations



- Asthma managed by current British Thoracic Society guidelines vs #s of sputum eosinophils
- Increased eosinophils "predict" exacerbation-related disease
- Low eosinophils in sputum predict few exacerbations and lower ICS dose

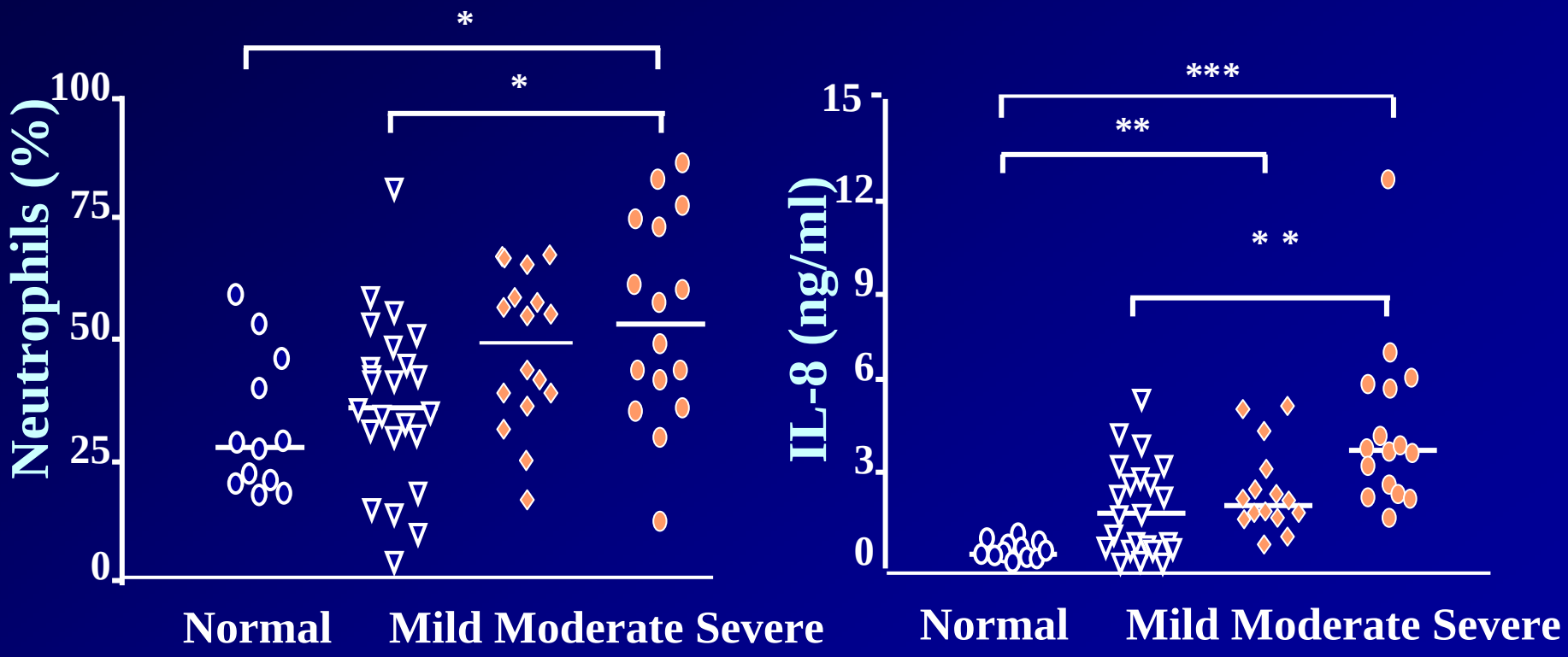
Green. Lancet 2002

Fe_{NO} increased with eosinophilic inflammation



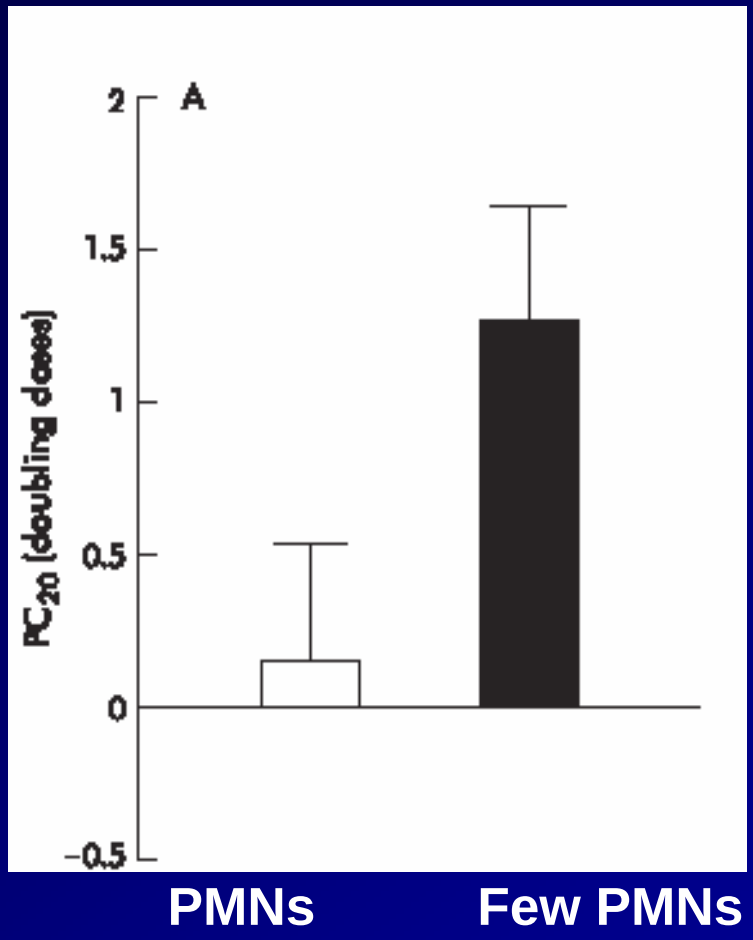
Silkoff et al., J Allergy Clin Immunol 2005116:1249-55.

Neutrophilic asthma: General increase with severity



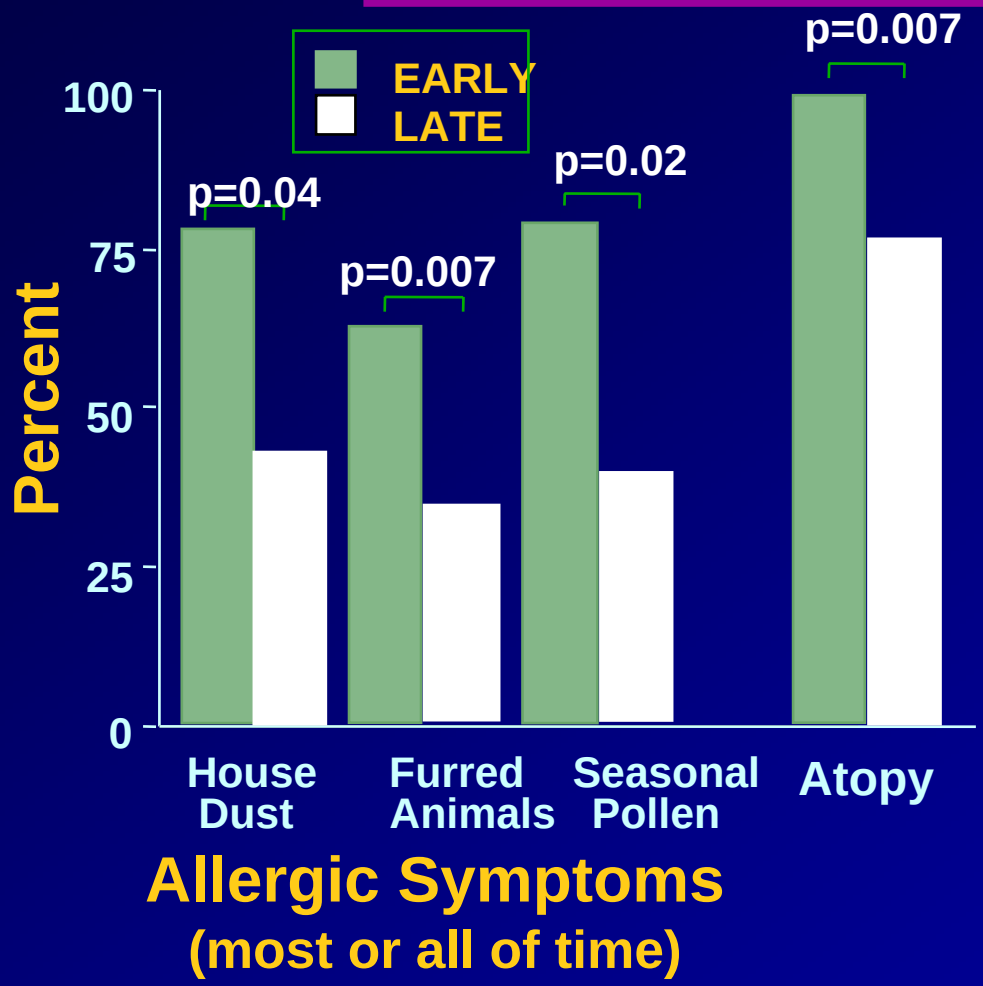
Jatakanon, et al.
Am J Respir Crit Care Med 1999

Neutrophilic inflammation poorly responsive to CSs



- Abundant neutrophils in sputum may limit response to CS
- Increased in smoking asthmatics
  - Green, Thorax 2002

III. Asthma Triggers: Allergic asthma/early onset disease



Hx eczema (p<0.001)

Early 40% Late 4%

Higher serum IgE

Family hx of asthma

Early>late

More lymphocytic

Th2? inflammation

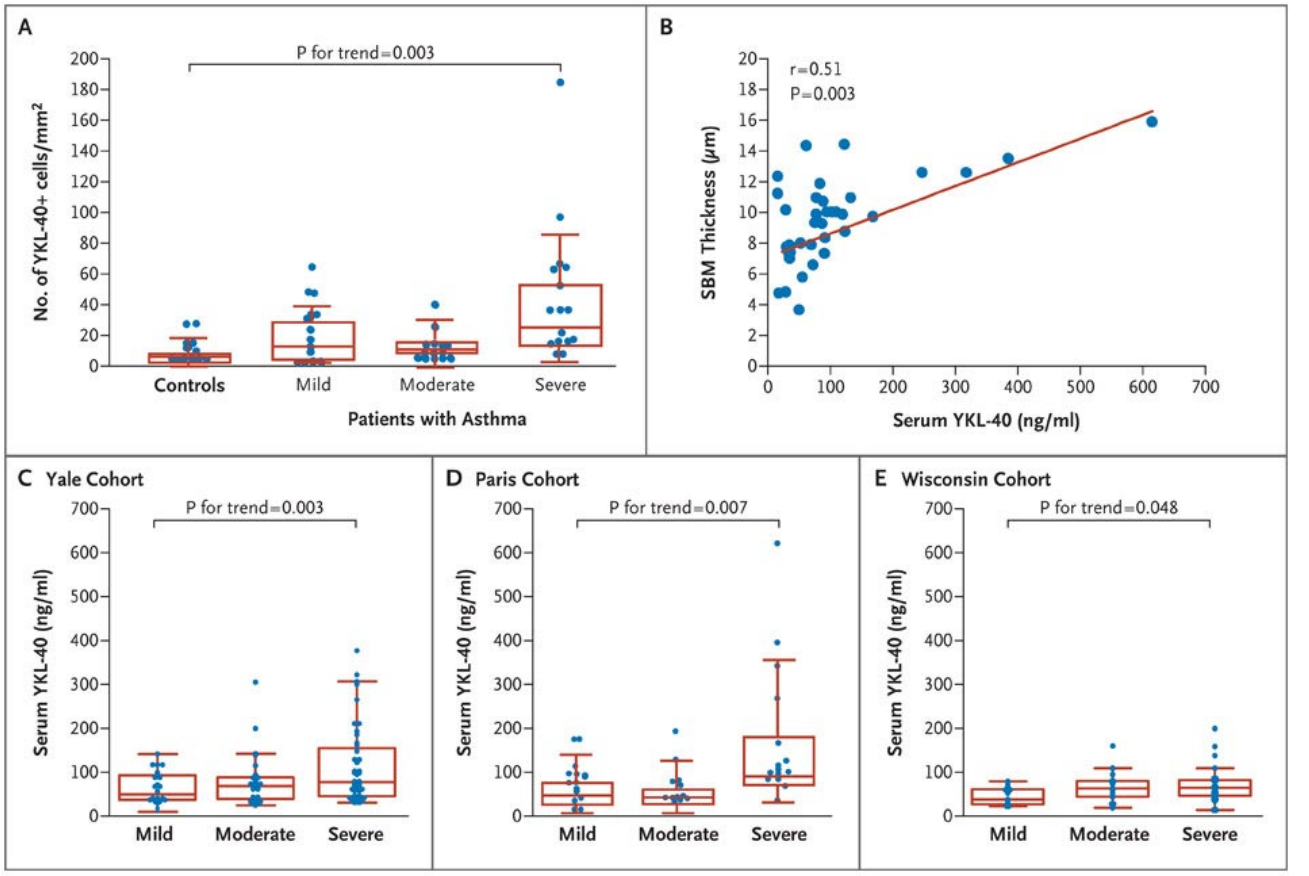
Miranda, J Allergy Clin Immunol Jan 2004

Mold allergy: Predicts more severe disease

Allergen	Asthma, no admission (n=82)	Asthma, 2+ admission (n=46)
Aspergillus	7 %	37 %
Alternaria	5 %	26 %
Cladosporium	1 %	41 %
Penicillium	2 %	30 %
Candida	10 %	33 %
Any fungal allergen	16%	76%

O'Driscoll et al, BMC Pulmonary Medicine 2005;5:4

Role of Chitinases: "Very trendy"…

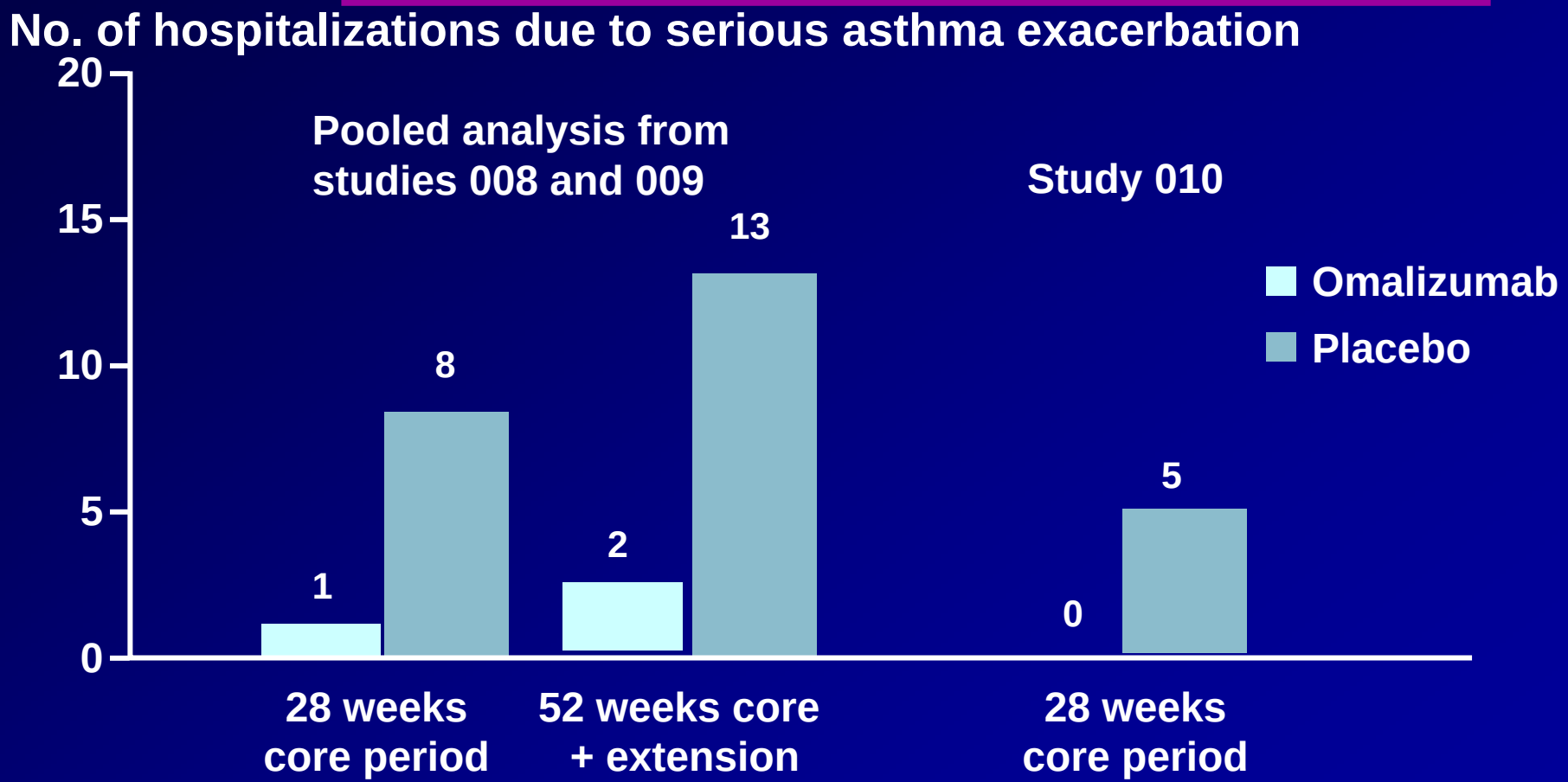


While AMCase has chitinase activity, YKL-40, and most others in humans, do not. Therefore, link between fungal/ insect allergens, still unclear

Chupp G et al. N Engl J Med 2007;357:2016-2027

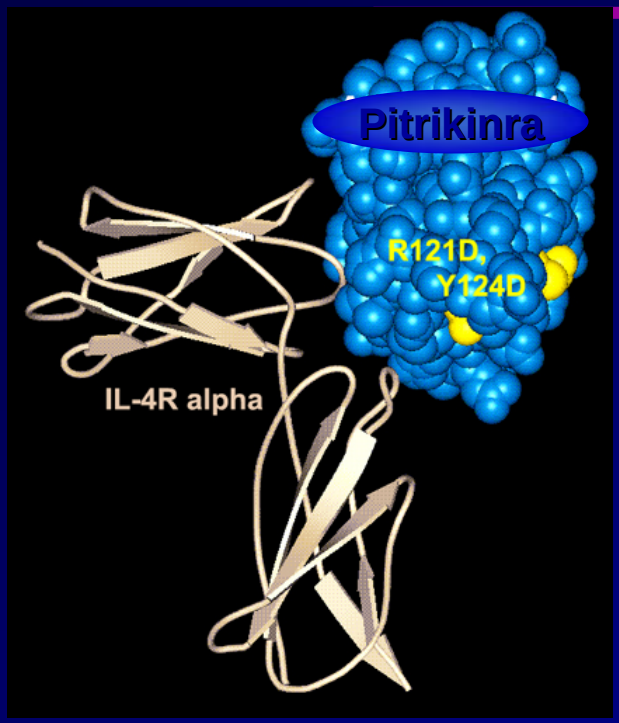
The NEW ENGLAND JOURNAL of MEDICINE

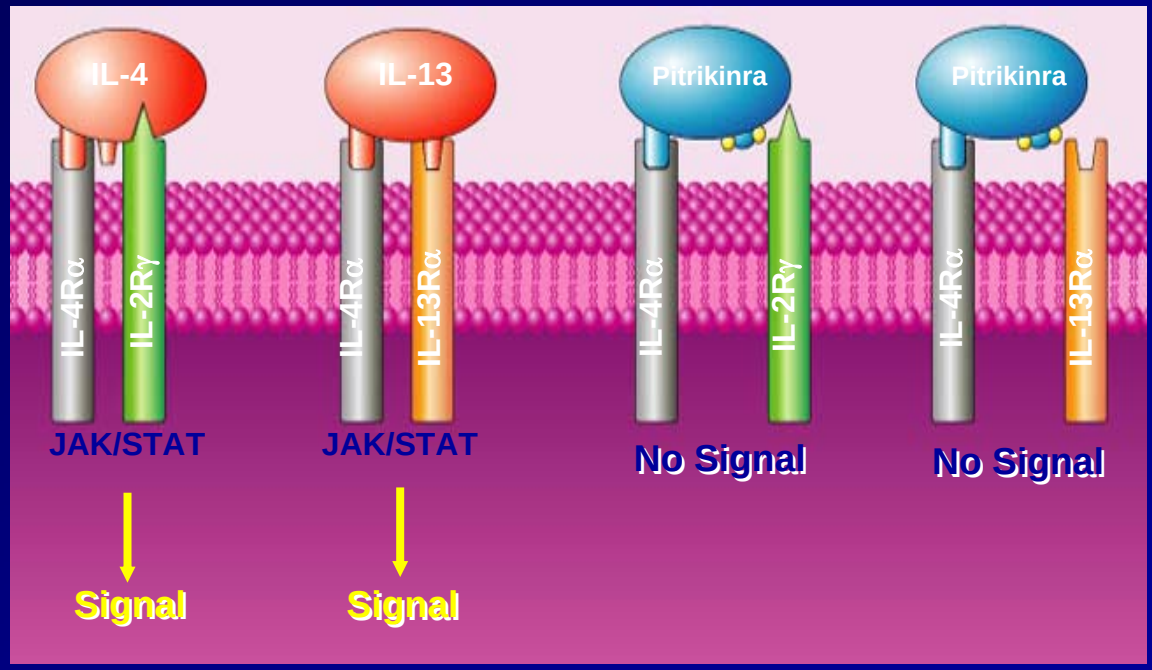
Allergic asthma may respond better to anti-IgE Rx



Busse W, et al. *J Allergy Clin Immunol.* 2001;108:184-190; Soler M, et al. *Eur Respir J.* 2001;18(2):254-261.

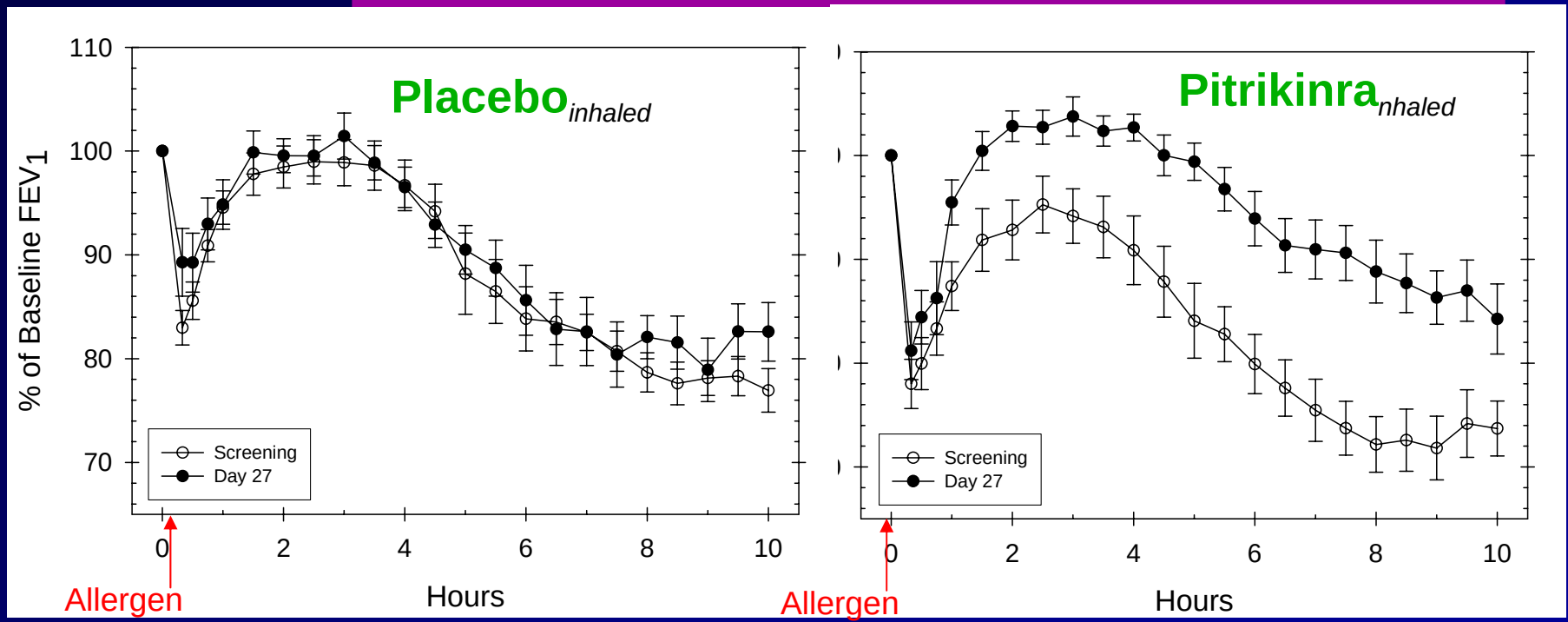
Th2 intervention improves allergic responses in mild asthma





Pitrikinra is a 14 kDa IL-4 mutein that inhibits assembly of IL2Rγ or IL13Rα into receptor complexes with IL-4Rα

Pitrikinra decreases *allergen induced exacerbation*



3.7-fold reduction in average LAR FEV_1 %fall from pre-challenge baseline

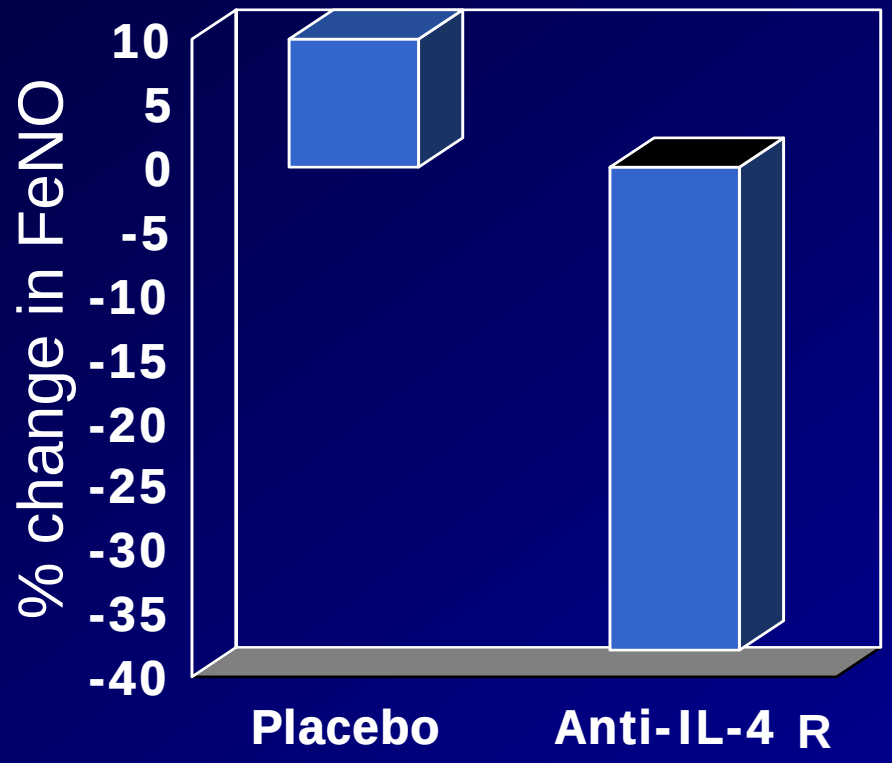
95% CI on ratio of ANCOVA-adjusted means, placebo / AEROVANT = (2.1, 6.3)

p < 0.001

Mean ± SEM (n = 14 placebo, 15 AEROVANT)

Wenzel, Lancet, October 2007

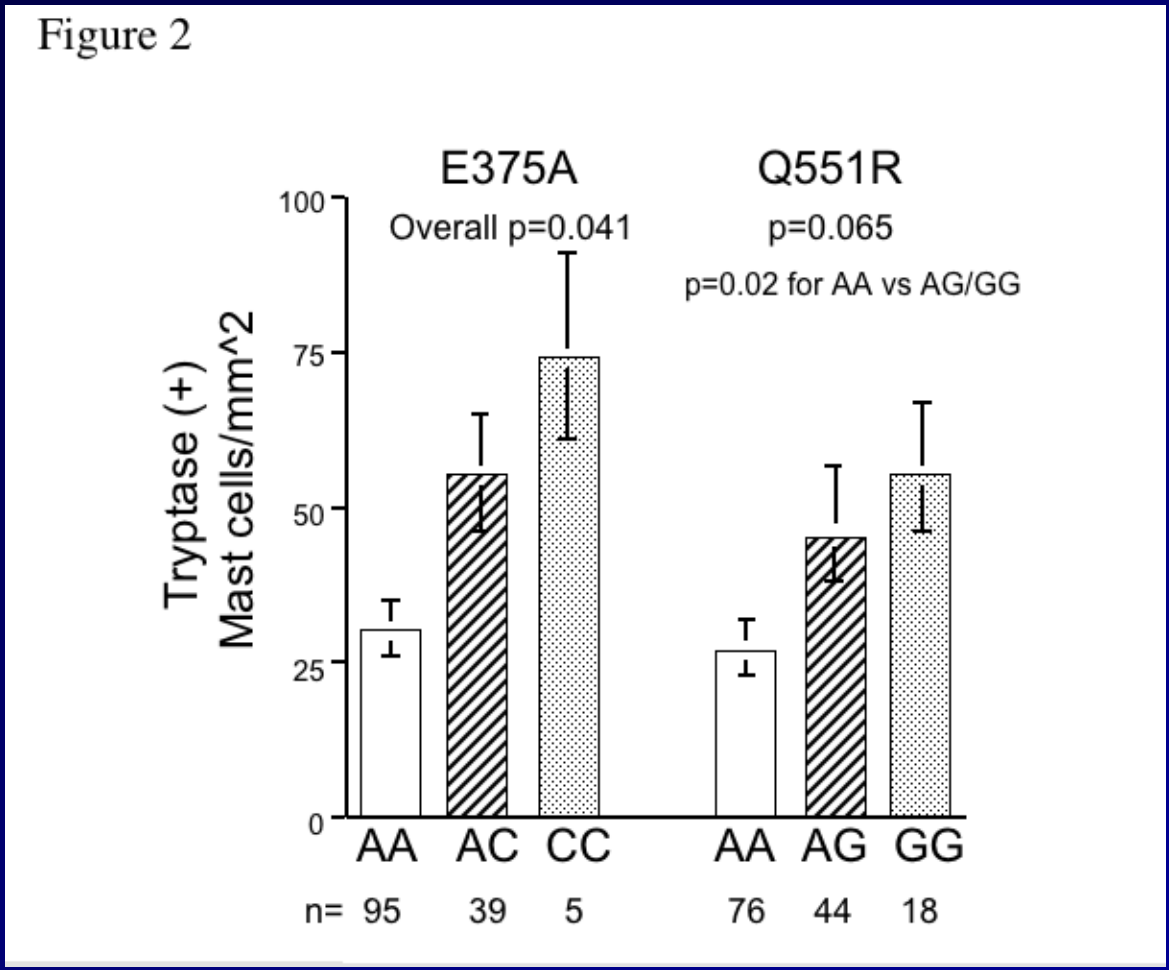
Inhibition of IL-4Rα pathway improves allergic inflammation



- Blocking IL-4Ralpha decreased FeNO at baseline and tended to decrease FeNO after allergen challenge
- Studies in atopic derm showed effect on IgE as well
- Same IL-4R genotypes identified with risk/inflammation may respond best to Rx

Wenzel, the Lancet Oct 2007

IL-4Rα genotypes also associate with increased mast cells



C allele for E375A associated with greater # and % of IgE (+) cells *in airways*

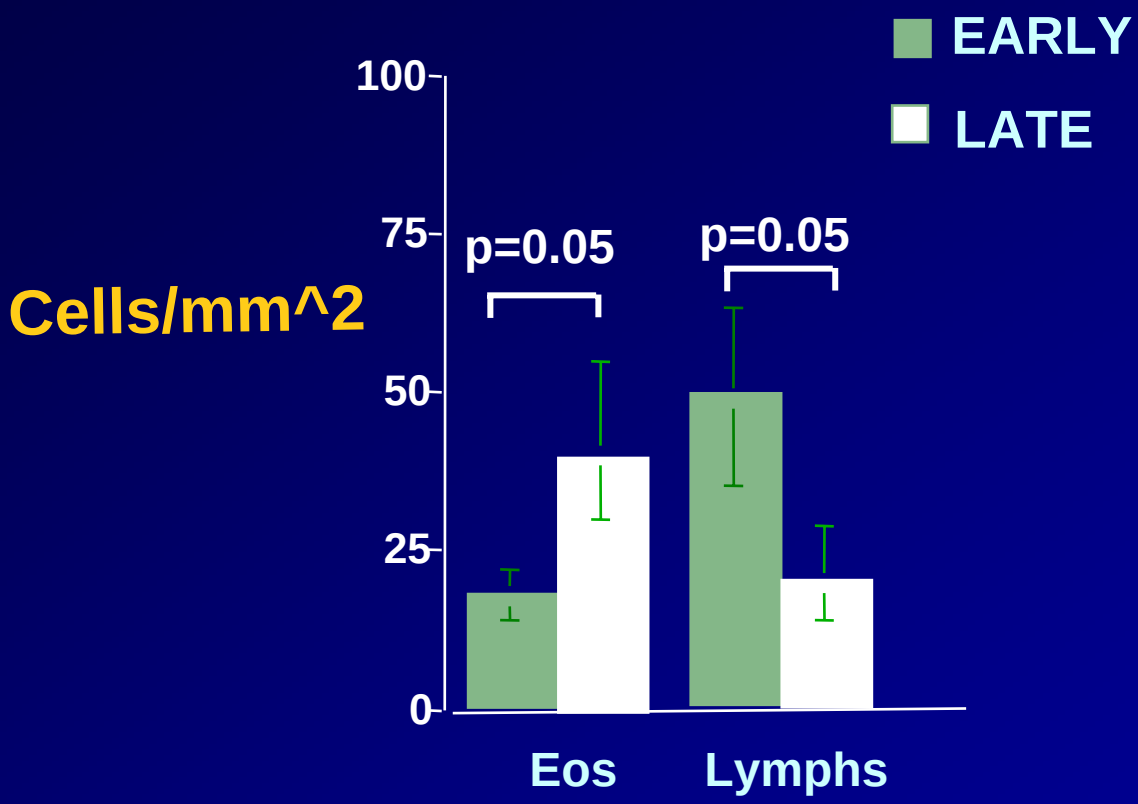
High IgE (+) mast cells *in airways* risk factor for high intensity exacerbations

Balzar JACI 2007

Late onset: “Aspirin sensitive-like”

- Adult onset eosinophilic asthma
- May or may not have hx of exacerbation in response to NSAID
- Often with sinusitis, sometimes bronchiectasis
  - Some patients appear to respond to anti-fungal Rx but don’t meet criteria for ABPA
- Association with occupational exposure?
- Highly eosinophilic (more so than allergic/early onset) Miranda 2004/SARP
- Rx implications: LTRA/5 LO inhibitor…maybe anti-TNF-alpha and maybe anti-fungals

Eosinophils in tissue more common in late onset disease



Miranda JACI 2004

Likely reflection of more aspirin sensitive-like asthma

Late onset disease: higher urinary LTE4 levels p=0.009

Sputum eos higher in late onset asthma:SARP

Randomised trial of itraconazole in ABPA - results

Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

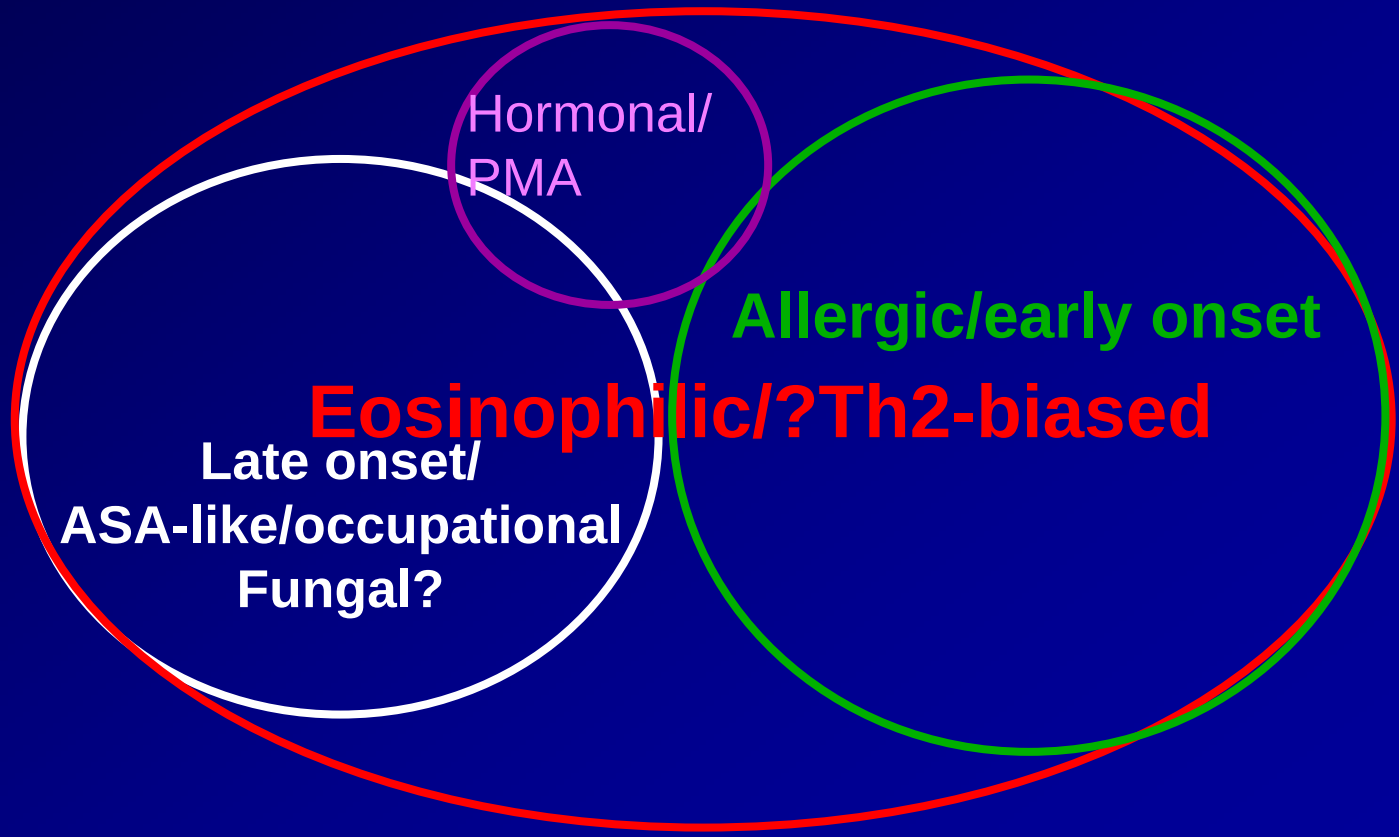
	Itra	Placebo then Itra	
Phase 1			
Overall response	13/28 (46%)	5/27 (19%)	p=0.04
Phase 2			
No prior response (n=33)	4/13 (31%)	8/20 (40%)	NS

Stevens D A et al, New Engl J Med 2000; 342:756

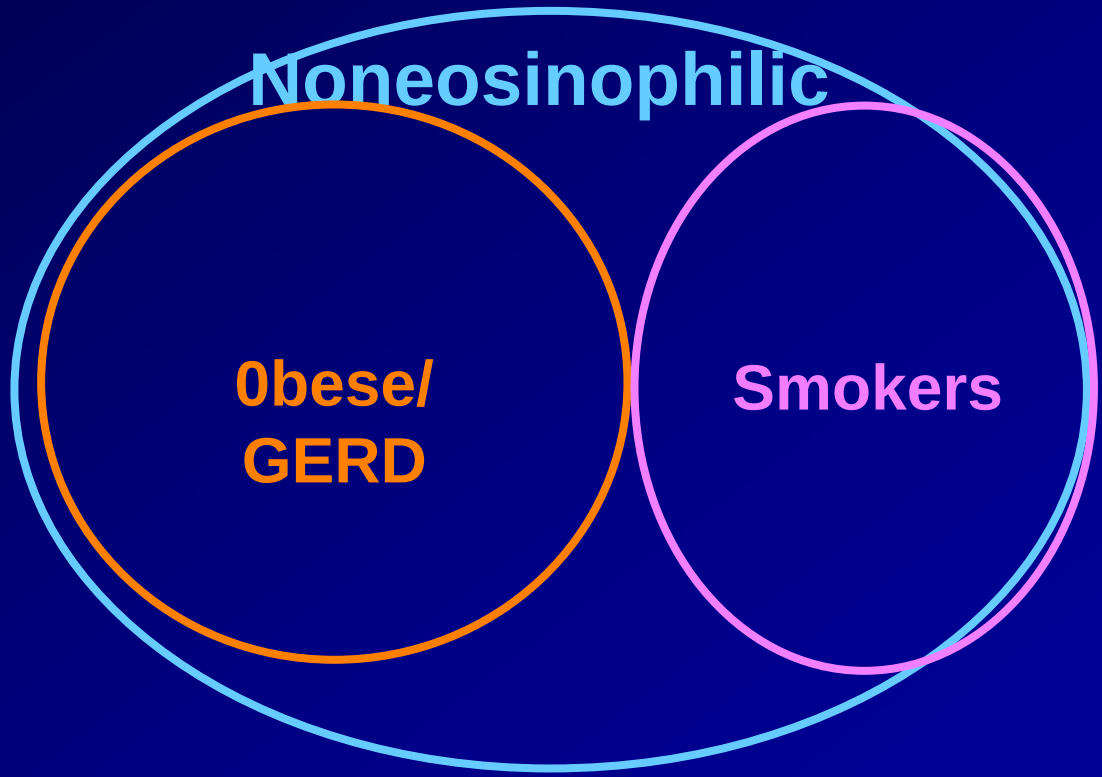
Others

- Premenstrual/hormonal
  - Role of genetic factors
    - Severe female asthmatics: lower PGE2/15 PGDH levels
  - Role for hormonal manipulation?
- Distal lung inflammation
  - Fine particle aerosols/systemic anti-inflammatories
- Obesity
  - Strong association with GERD
  - Non-eosinophilic/non-Th2 asthma may respond to weight loss strategies
- Smoking
  - Smoking cessation

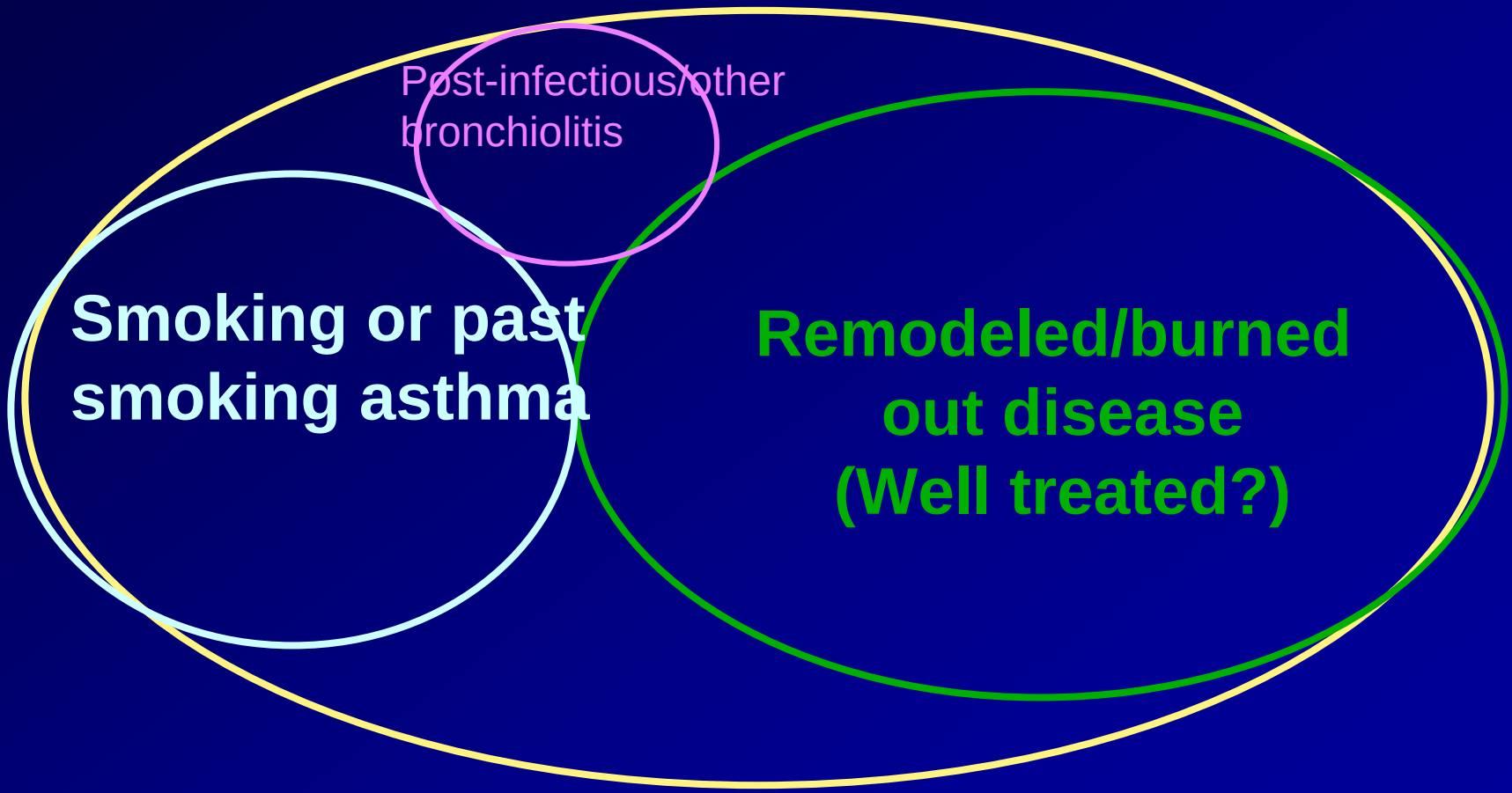
Exacerbating: Eosinophilic/steroid responsive



Exacerbating: Less steroid responsive



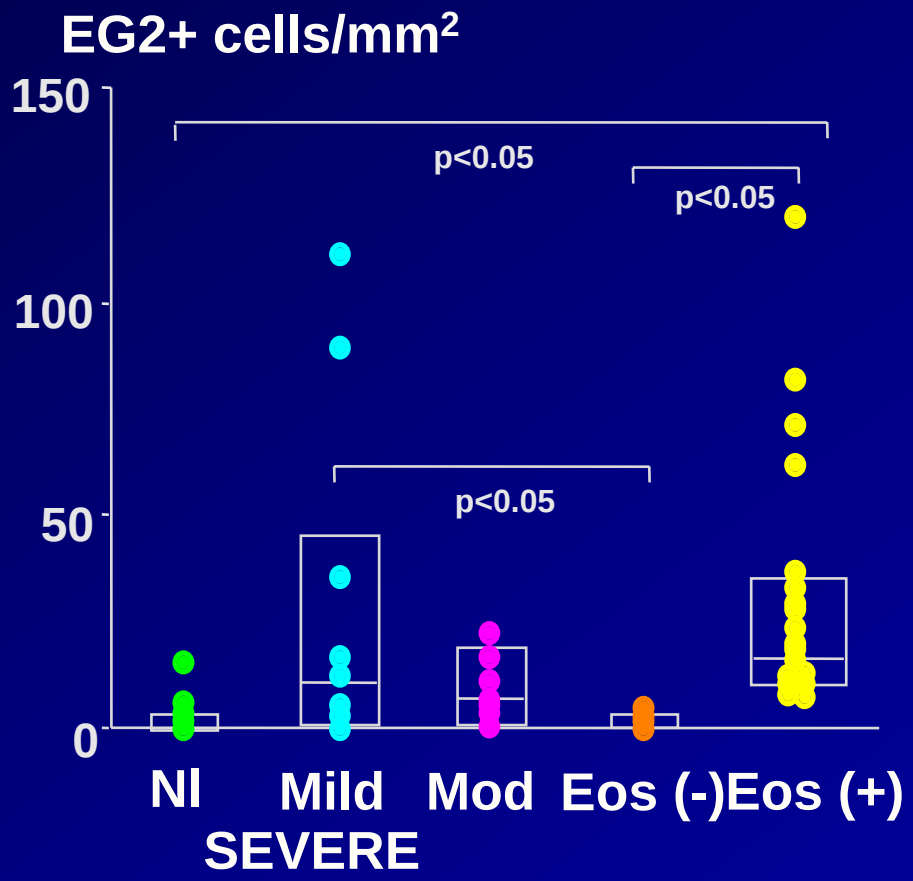
Progressive/stable airflow limitation



However...

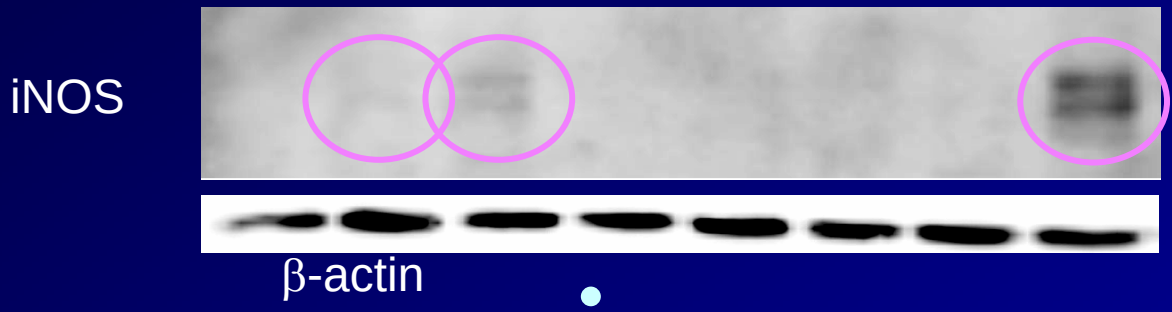
- Those with FEV1 decline had no more or less use of steroids
- Had LESS health care utilization (hospitalizations) than those without decline in FEV1
- Had no difference in PC20 compared to those that did not decline

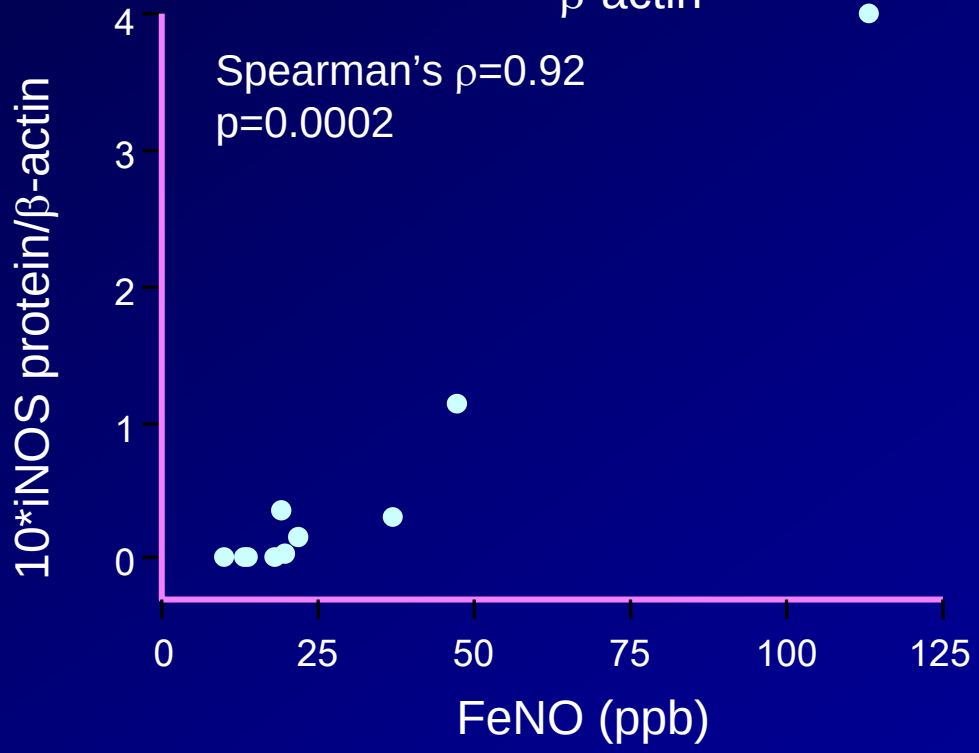
Eosinophils not found in all asthma tissues



Wenzel et al., Am J Respir Crit Care Med 1999;160:1001-08.

In vivo, iNOS protein highly correlated with Fe_{NO}





iNOS protein increases with severity, while FeNO does not