

Phenotypes of Severe Asthma

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Current Asthma Therapy: Little Need to Phenotype

- * Most mild and to some degree moderate asthmatics respond well to currently available therapies
- * Implies mild asthma homogeneous disease and/or therapies quite nonspecific

ATS-ERS Task Force on Outcomes: Start with Difficult Asthma

DIFFICULT ASTHMA
 (i.e. requiring high intensity treatment)

Good control only if on high intensity Rx	Poor control despite high intensity Rx
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Initial Subtyping

NO ASTHMA
 (VCD, Obesity, malingering)

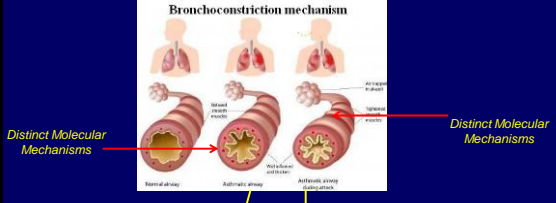
Potentially treatment-responsive
 e.g. poor compliance, persisting allergen exposures, smoking etc

Persistent co-morbidities
 e.g. persistent sinusitis, psychosocial problems, obesity
 Treating GERD phenotype of ? impact

Treatment-resistant
 (sometimes called "refractory asthma")

Adapted from Taylor DR ERJ 2008

Bronchoconstriction mechanism



Distinct Molecular Mechanisms

Cellular/pathological/physiologic features underlying phenotype A

Clinical Phenotype A

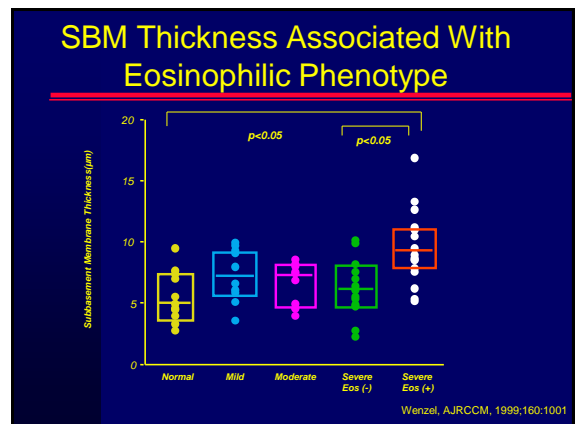
Cellular/pathological/physiologic features underlying phenotype B

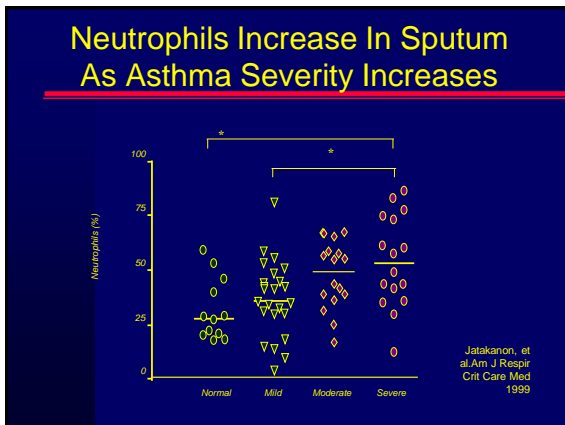
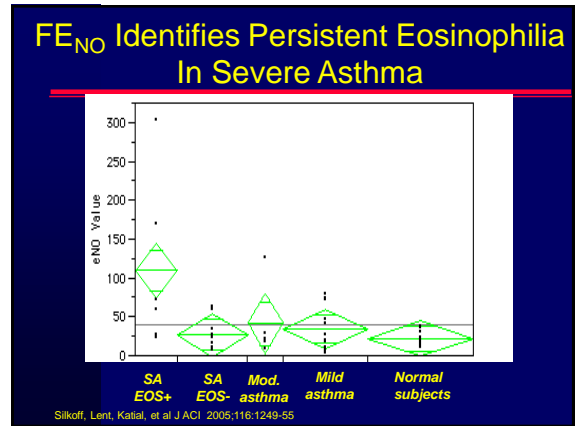
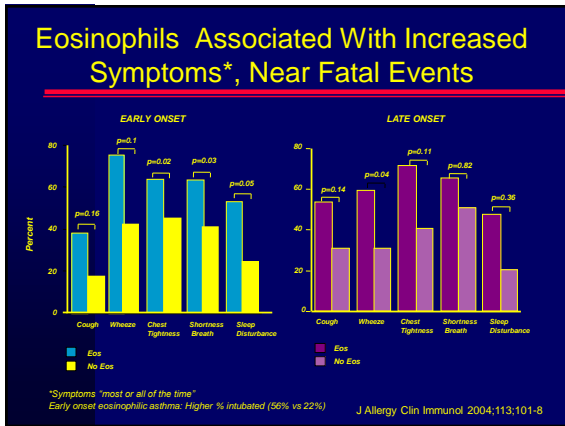
Clinical Phenotype B

Recognizable Disease Syndrome

Cellular Phenotypes

- * Eosinophilic
- * Neutrophilic
- * Pauciimmune

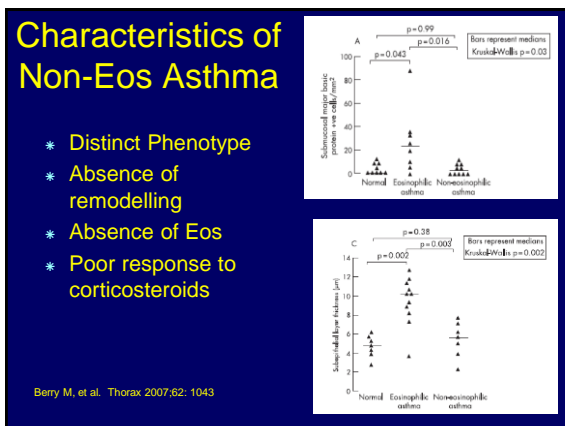




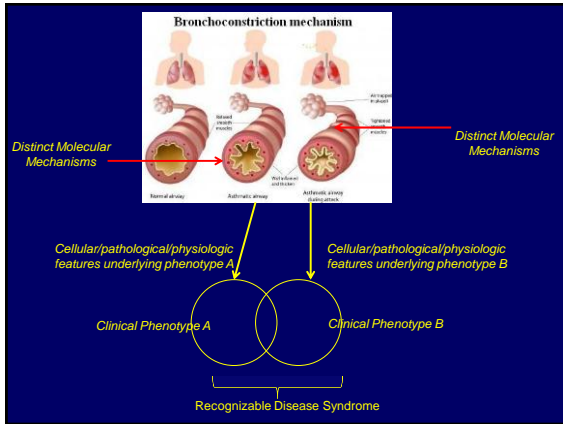
Sputum Cell Counts

- * Average cell counts (partial data – subset of baseline samples from each group):

Group	Total cell counts (million)	Eos percent	Neut percent
Non-asthmatic controls	4.63	2.4%	44.4%
Well-controlled asthmatics	2.75	0.9%	19.1%
Not well-controlled asthmatics	4.08	1.7%	40.8%
Poorly controlled asthmatics	4.43	2.5%	74.8%

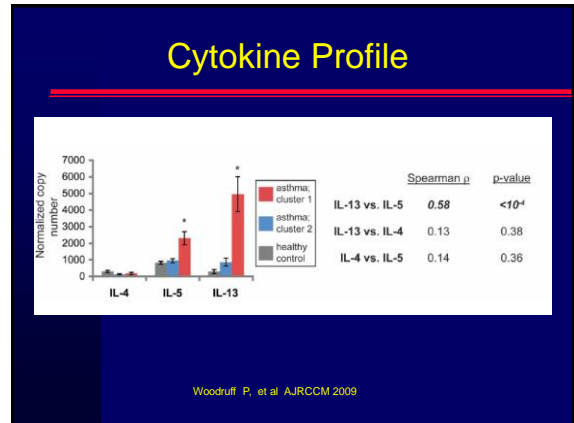
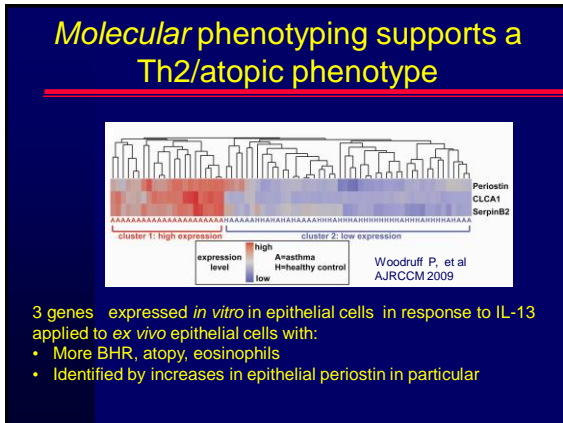


- ### Neutrophilic Asthma
- * Consistently associated with CS use and low FEV1
 - Lesser response to CSs *Green, Thorax 2002*
 - More airway wall thickening and air trapping on CT *Gupta Chest 2009, Busacker Chest 2009*
 - * SARP clusters suggested most severe and poorly reversible (to normal) late onset cluster also the most neutrophilic
 - Some neutrophilic asthma may be just CS treated allergic/Th2 asthma



"Th2" vs "Th2-Lo" asthma

- * Since inception of Th1/Th2 concept, asthma thought of as Th2, primarily allergic, disease
- * Vast majority of animal models use some variation of Th2 immunity
- * "Classic" allergic asthma likely makes up bulk of "asthma" or dominant phenotype. Driven partially by Th2 cytokines IL-4, IL-5, IL-13



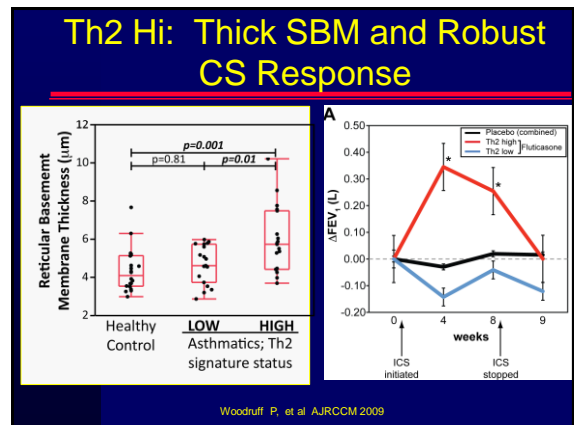
Features of Molecular Phenotypes

Both Th2 High and Low has:

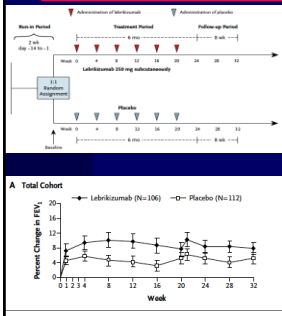
- * Decrements in FEV1
- * Bronchodilator responsiveness
- * Skin Prick test reactivity

Th2 High has greater:

- * AHR
- * IgE
- * Blood and BAL Eosinophilia



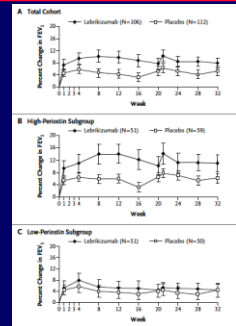
Th2 Phenotyping & Treatment of Severe Asthma



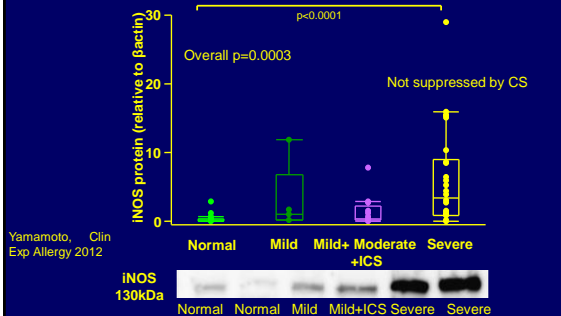
- * 200+ pts with moderate to severe asthma on mid to high dose ICS, most with LABA randomized to Rx with anti-IL-13 vs placebo
 - * Anti-IL-13 modestly effective in improving FEV1 in all comers
 - * However, 2ndary analysis was to target "Th2 Hi vs LO"
- Corren, et al N Engl J Med 2011

Serum Periostin Identifies Th2 Hi Phenotype Which Responds to Anti-IL-13

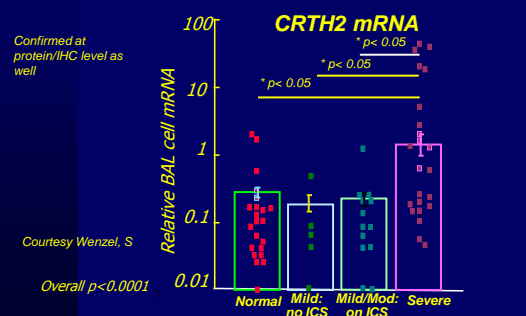
- * Patients divided by median split of periostin levels
- * Those with hi periostin had the largest increase in FEV1
- * Hi FeNO as good or better than periostin



Lack of iNOS response to high dose CS: FeNO as biomarker for Th2 severe asthma

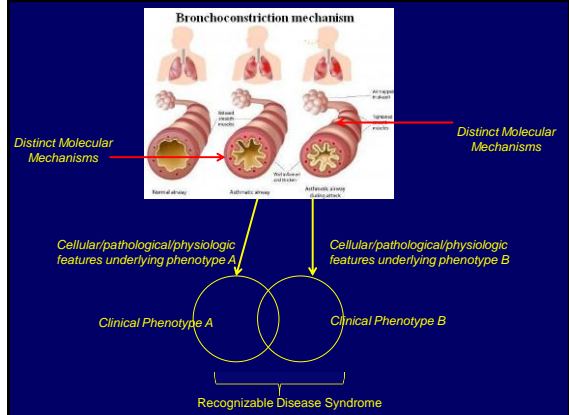


PGD2 Receptor, CTRH2, Selectively Increased in Severe Asthma

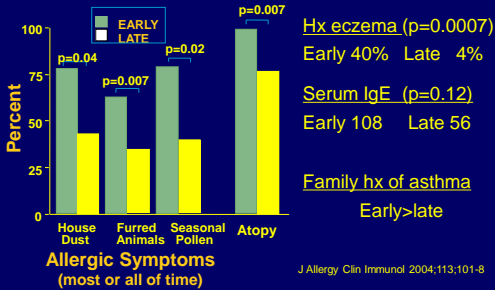


"Th2-Lo Asthma"

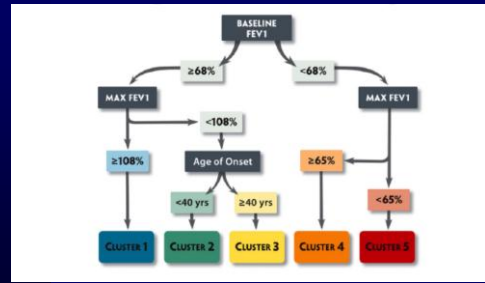
- * Defined as the "apparent" absence of Th2
- * Much less well defined than Th2-Hi
- * Generally adult onset
- * May include neutrophilic, obesity-related, post infectious, smoking related?
- * All associated with poor CS response



Early onset asthma: Identifies an "allergic"/Th2 phenotype

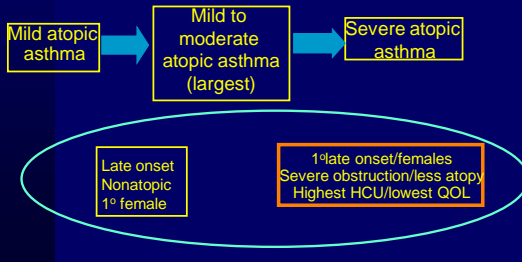


SARP Cluster Analysis

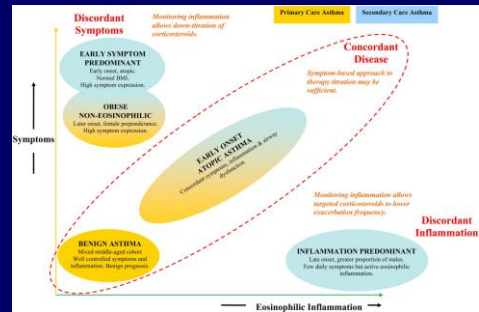


Moore et al. Am J Respir Crit Care Med 2010;181:315-23

SARP clusters: 50% of severe asthma late onset, less allergic



Obese Asthmatics May Be a Distinct Subset

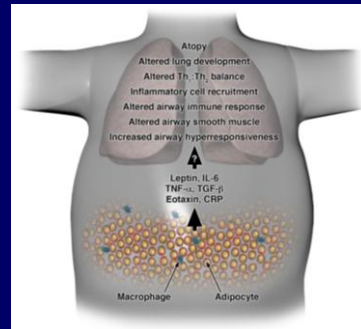


Haldar P et al. Am J Respir Crit Care Med 2008;178:218-24

Obesity

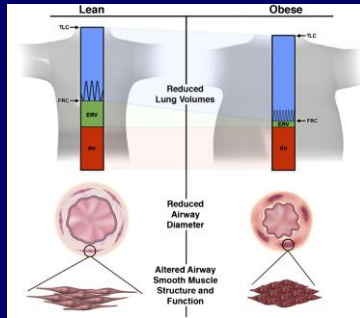
- * Controversial phenotype
- * Studies suggest highly symptomatic and high HCU
- * Diagnosis of asthma not clear in some cases Parkvale Chest 2010
- * As a phenotype more strongly associated with late onset asthma Haldar AJRCCM 2008, Moore AJRCCM 2010, Holguin JACI 2011

Obesity and Airway Inflammation



Beutner DA et al. Am J Respir Crit Care Med 2006;174:112-119

Mechanical Effects of Obesity



Beuther DA et al. Am J Respir Crit Care Med 2006;174:112-119

Obesity and Asthma Key Clinical Observations

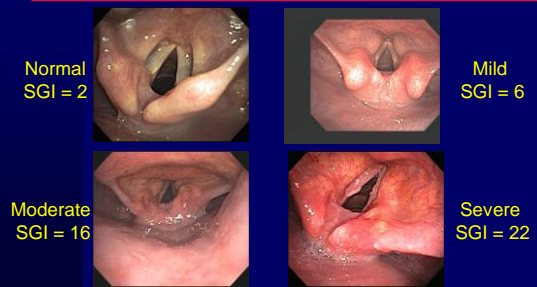
- * 250,000 new asthma cases/year due to obesity
- * BMI a differentiator of asthma phenotype
- * Obesity reduces glucocorticoid sensitivity
- * Obesity alters macrophage phenotype/function
- * Vitamin D may be an important cofactor
- * No specific recommendations in NAEPP or GINA regarding the treatment of obese asthmatics

Refractory Asthma: Importance of Bronchoscopy to Identify Phenotypes and Direct Therapy

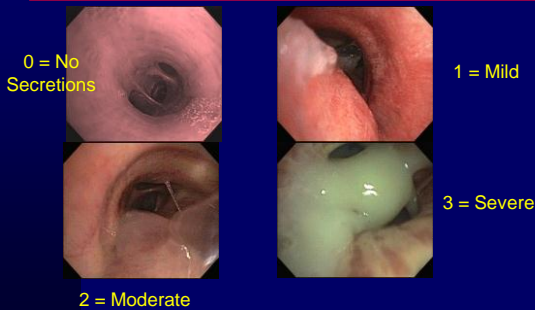
- * ≥ 18 y/o, n = 58
- * 12% improvement post BD or PC20 ≤ 6 mg/ml
- * Met ATS criteria for refractory asthma
- * Exclusion
 - Smoking history > 5 pack years
 - Evidence of VCD by history or flow-volume loops compatible with VCD

Chest 2012 Mar;141(3):599-606

Different Degrees of Upper Airway Pathology



Lower airway: Secretions



Initial 20 Patients Intensified Standard vs Directed Treatment

