



**Adult asthma diagnosis and treatment**

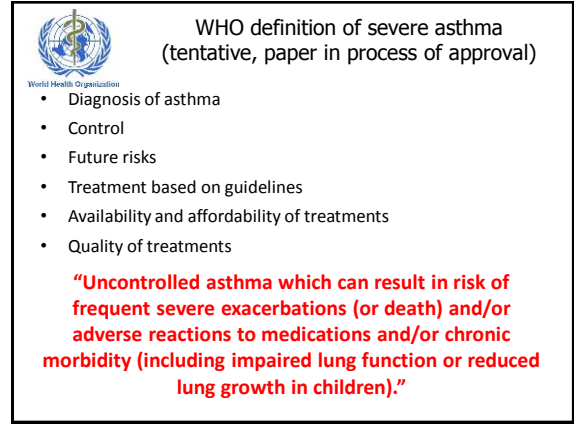
Stephen T Holgate,  
Faculty of Medicine,  
University of Southampton,  
UK

sth@soton.ac.uk

Decreased responsiveness of epithelium to inhaled environmental agents and inflammation by cell products

Smooth muscle

Top: High peak flow, low variability; Bottom: Low peak flow, high variability

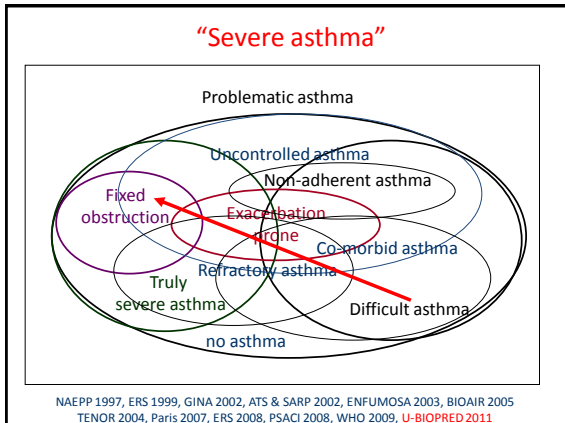


**WHO definition of severe asthma**  
(tentative, paper in process of approval)

World Health Organization

- Diagnosis of asthma
- Control
- Future risks
- Treatment based on guidelines
- Availability and affordability of treatments
- Quality of treatments

**“Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).”**



**“Severe asthma”**

Problematic asthma

Uncontrolled asthma

Non-adherent asthma

Fixed obstruction

Exacerbation-prone

Refractory asthma

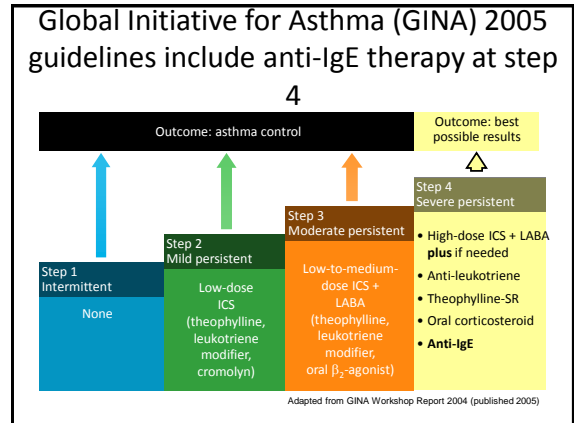
Truly severe asthma

Comorbid asthma

Difficult asthma

no asthma

NAEPP 1997, ERS 1999, GINA 2002, ATS & SARP 2002, ENFUMOSA 2003, BIOAIR 2005, TENOR 2004, Paris 2007, ERS 2008, PSACI 2008, WHO 2009, U-BIOPRED 2011



**Global Initiative for Asthma (GINA) 2005 guidelines include anti-IgE therapy at step 4**

4

Outcome: asthma control

Outcome: best possible results

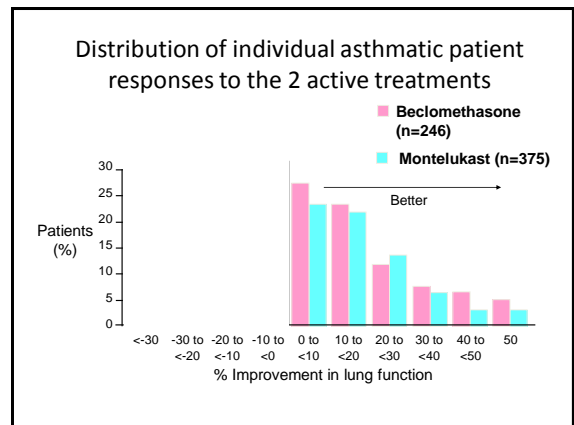
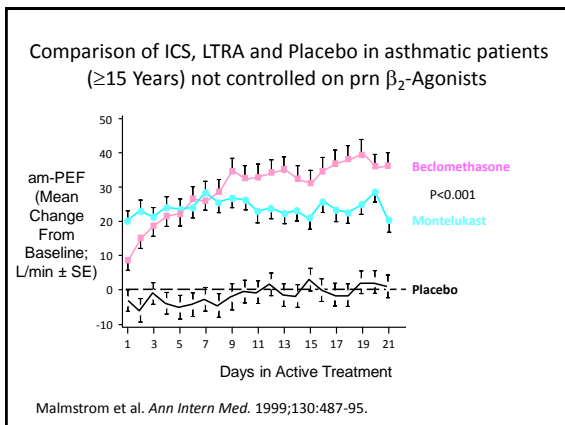
Step 1 Intermittent: None

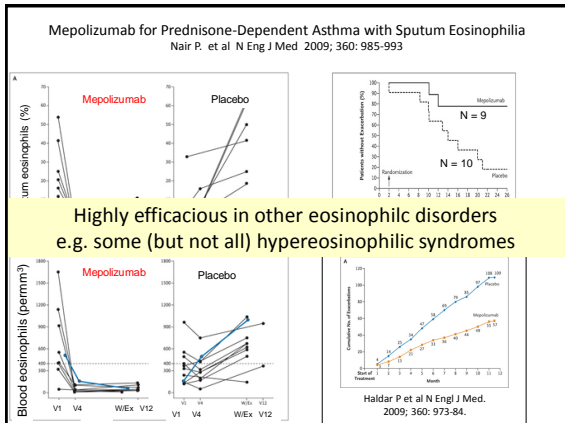
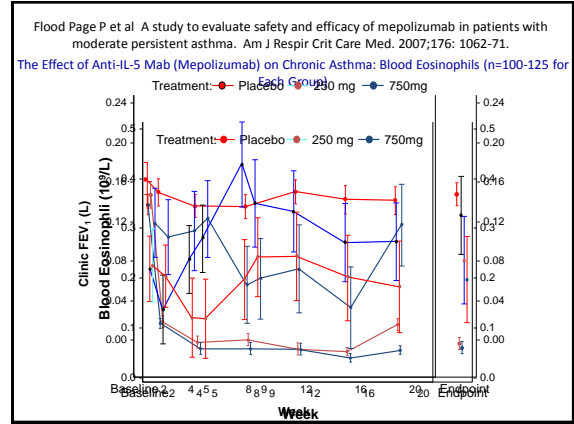
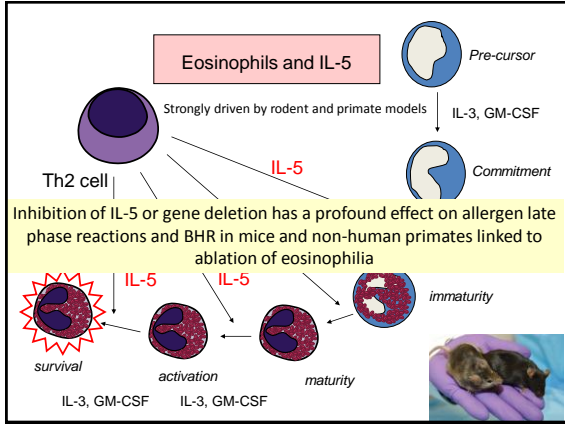
Step 2 Mild persistent: Low-dose ICS (theophylline, leukotriene modifier, cromolyn)

Step 3 Moderate persistent: Low-to-medium-dose ICS + LABA (theophylline, leukotriene modifier, oral  $\beta_2$ -agonist)

Step 4 Severe persistent: High-dose ICS + LABA plus if needed, Anti-leukotriene, Theophylline-SR, Oral corticosteroid, **Anti-IgE**

Adapted from GINA Workshop Report 2004 (published 2005)



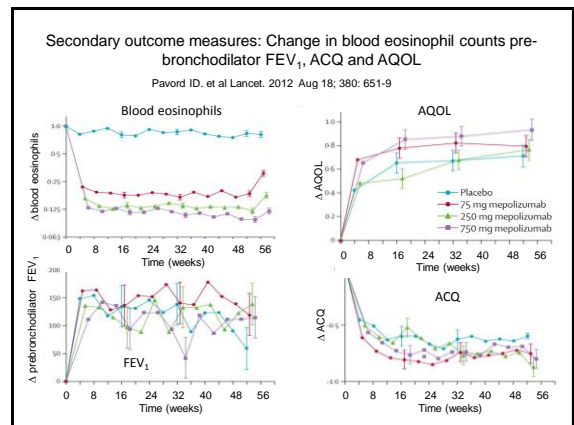
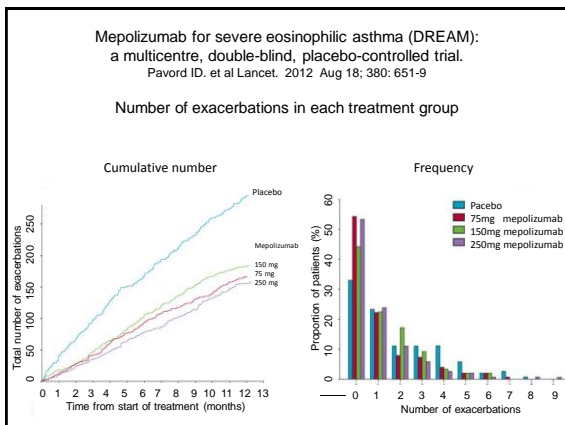


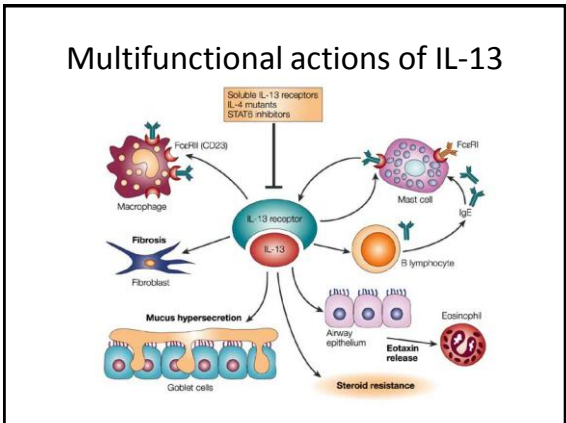
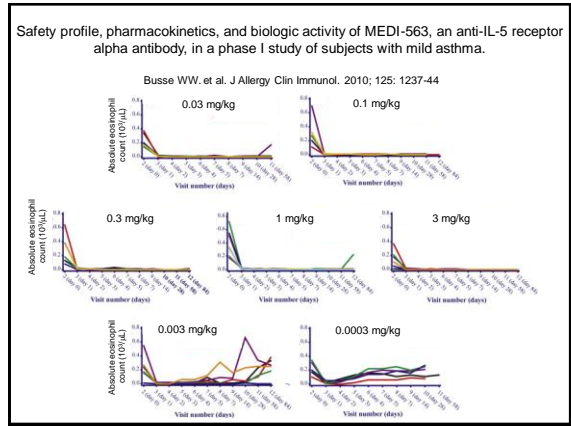
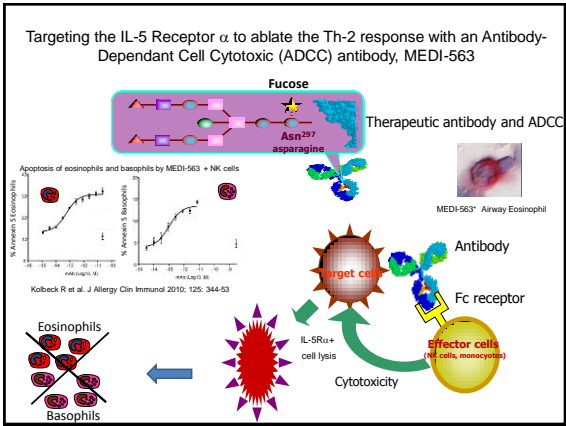
Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.

Pavord ID. et al Lancet. 2012 Aug 18; 380: 651-9

- 621 asthmatic patients with a history of recurrent severe asthma exacerbations, and ongoing eosinophilic inflammation randomised iv mepolizumab (75 mg, 250 mg, or 750 mg) or placebo; 13 infusions at 4-week intervals.
- Primary outcome: rate of clinically significant asthma exacerbations requiring oral corticosteroids, admission, or a visit to an emergency department.
- Rate of clinically significant exacerbations was 2.40 per patient per year in the placebo group, 1.24 in the 75 mg group (48% reduction), 1.46 in the 250 mg group (39% reduction) and 1.15 in the 750 mg group (52% reduction).

Mepolizumab is an effective and well tolerated treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma.





Pubmed: IL-13 publications up to 2010

All entries: 2968  
Allergy: 1000  
Asthma: 742  
Animal/asthma: 417  
Mouse/asthma: 347  
Human: 66 (reviews 52)  
Human sputum or biopsy: 6 (2 reviews)

Original research:

**Increased sputum and bronchial biopsy IL-13 expression in severe asthma.**  
Saha SK, Berry MA, Parker D, Siddiqui S, Morgan A, May R, Monk P, Bradding P, Wardlaw AJ, Pavord ID, Brightling CE. J Allergy Clin Immunol. 2008 Mar;121(3):685-91.

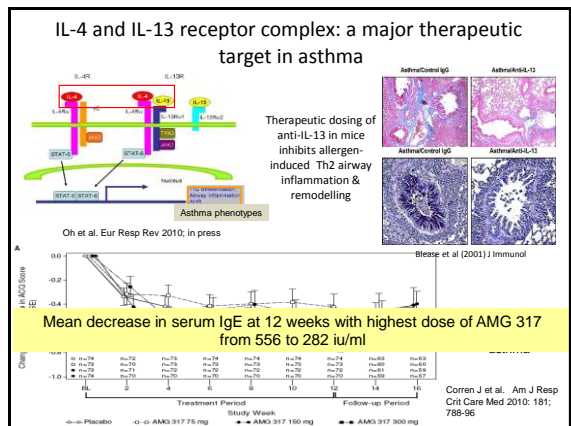
**Sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis.**  
Berry MA, Parker D, Neale N, Woodman L, Morgan A, Monk P, Bradding P, Wardlaw AJ, Pavord ID, Brightling CE. J Allergy Clin Immunol. 2004 Nov;114(5):1106-9

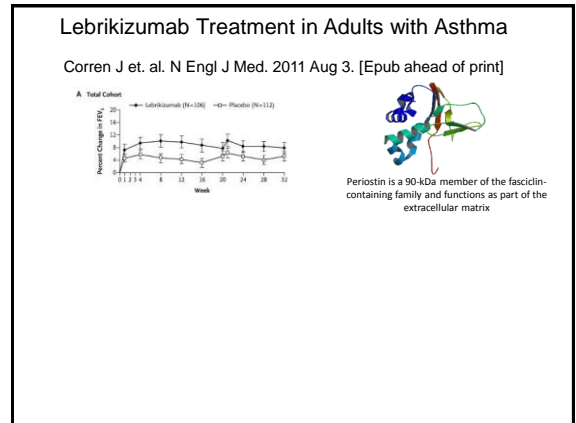
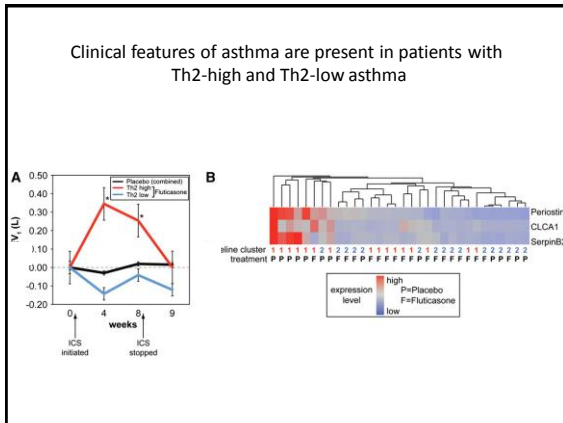
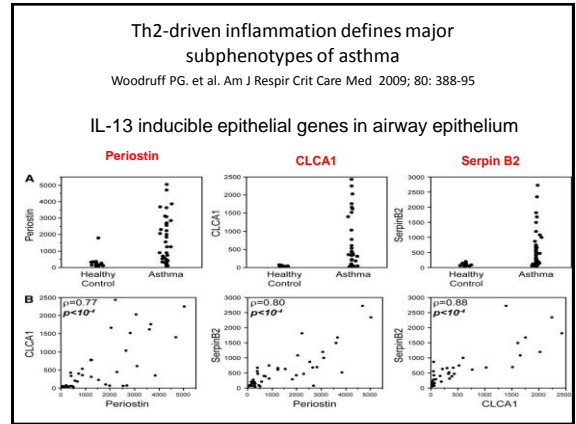
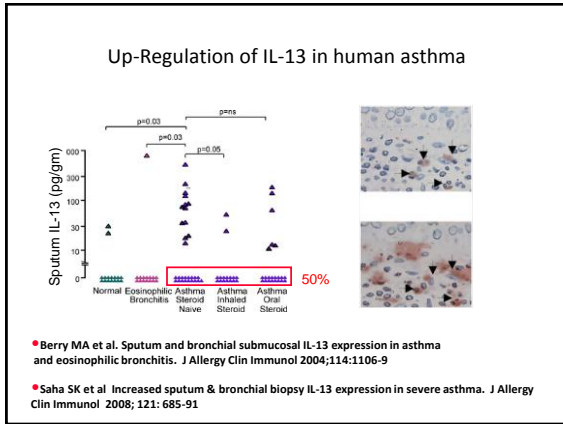
**Inflammatory biomarkers in airways of patients with severe asthma compared with non-severe asthma.**  
Macedo P, Hew M, Torrego A, Jouneau S, Oates T, Durham A, Chung KF. Clin Exp Allergy. 2009 Nov;39(11):1668-76.

**Immuno-regulatory cytokines in asthma: IL-15 and IL-13 in induced sputum.**  
Komal-Koma M, McKay A, Thomson L, McSharry C, Chalmers GW, Liew FY, Thomson NC. Clin Exp Allergy. 2001 Sep;31(9):1441-8

Biotherapeutics: targeting IL-13 and IL-4: a massive investment by industry

Candidate	Specificity	Format	Preclinical	I	II	III
<b>Nuvance (Immunex)</b>	IL-4	sIL-4R	Discontinued			
<b>Pitrakinra (Aerovance)</b>	IL-4R $\alpha$	IL-4 mutein				
<b>AMG-317 (AMGEN)</b>	IL-4R $\alpha$	mAb				
<b>QAX-576 (Novartis)</b>	IL-13	mAb				
<b>CAT-354 (Medimmune)</b>	IL-13	mAb				
<b>IMA-638 (Wyeth)</b>	IL-13	mAb				
<b>TNX650 (Genentech)</b>	IL-13	mAb				
<b>IL-13R (Merck &amp; Roche)</b>	IL-13R $\alpha$ 1	mAb				
<b>DOM1000P</b>	IL-13	mAb fragment				
<b>DOM0910</b>	IL-4/IL-13	mAb fragment				
<b>UCB</b>	IL-4/IL-13	mAb fragment				





- Therapeutic targets in the allergic cascade that have so far failed to meet expectations in asthma clinical trials
- Mediators: histamine, prostaglandins (D<sub>2</sub>, F<sub>2α</sub>, TxA<sub>2</sub>) non-cysteinyil LTs (LTB<sub>4</sub>), tryptase, PAF, bradykinin, neuropeptides.
  - Cytokines: IL-4, -5, -9, 13, TNFα.
  - Chemokines: CCL3, eotaxin.
  - Adhesion molecules: α<sub>4</sub> (VCAM), ICAM-1, E selectin, P selectin.
  - Receptors: CD4, CD23 (low affinity IgE receptor), CD25 (IL-2 receptor).

### Stratified Medicine: What are we talking about?


“the tailoring of medical treatment to the individual characteristics of each patient .... involves the use of companion diagnostics to achieve the best outcomes in the management of a patient's disease or disease predisposition. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not”.

Adapted from: "Priorities for Personalized Medicine" by the US President's Council of Advisors on Science and Technology (PCAST), 2008

- Personalised Medicine has arrived to an extent:
  - Herceptin®, Gleevec®, Selznety™, Ziagen®, Vectibix®, Iressa™


**Toward Precision Medicine**  
Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

2011



Medicine will move from a reactive to a proactive discipline over the next decade; one that is predictive, personalised, preventive and participatory


treatment and prevention of disease (IPM)



THE NATIONAL ACADEMIES PRESS  
Washington, D.C.  
www.naap.edu

The promise of personalised medicine

- More effective medicines
- Safer medicines
- Cheaper medicines
- Better healthcare
- Cheaper healthcare
- Less (rather than more) healthcare disparity



**SARP Clinical Cluster Analysis**

- Cluster 1 Mild Allergic Asthma**  
Early onset; atopic; normal lung function  
≤ 2 controller medications; minimal health care utilization  
minimal sputum eosinophilia
- Cluster 2 Mild-Moderate Allergic Asthma**  
Most common cluster; early onset; atopic; borderline FEV1 but reverse to normal; ≤ 2 controller medications; low health care utilization, infrequent need for oral corticosteroids  
minimal sputum eosinophilia
- Cluster 3 More Severe Older Onset Asthma**  
Older; very late onset; higher BMI (obese); less atopic; slightly decreased FEV1 with some reversibility;  
frequent need for oral corticosteroids despite ≥ 3 controller medications including high doses of inhaled corticosteroids  
sputum eosinophilia
- Cluster 4 Severe Variable Allergic Asthma**  
Early onset; atopic; severely decreased FEV1, but very reversible to near normal; high frequency of symptoms and albuterol use; "variable" with need for frequent oral corticosteroids; high health care utilization  
sputum eosinophilia
- Cluster 5 Severe Fixed Airflow Asthma**  
Older; longest duration; less atopic; severely decreased FEV1 with less reversibility (COPD similarities); high frequency of symptoms and albuterol use despite oral corticosteroids; high health care utilization; co-morbidities  
Both sputum eosinophilia and neutrophilia

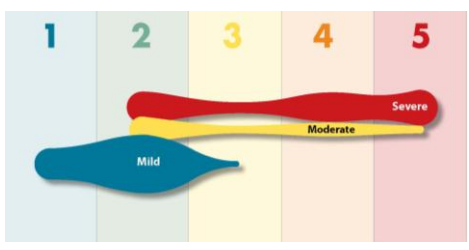
**Asthma Cluster Analysis: 5 Clusters**

- 1 Mild Allergic Asthma**  
Early onset asthma (EOA); Normal lung function; atopic  
≤ 2 Controller (medication use); Minimal Health Care Utilization (HCU); decreased sputum eosinophils (Eos)
- 2 Mild-Moderate Allergic Asthma**  
Most common cluster; EOA; Borderline normal FEV1 but reverses to normal; Atopic; ≤ 2 Controllers; Very low HCU, but some oral steroid bursts (OCS); ( decreased EOS)
- 4 Severe Variable Allergic Asthma**  
EOA; 53%; Severely decreased FEV1, but very reversible to near normal; Atopic OCS; "variable" with need for frequent OCS, High beta agonist use; HCU and global symptoms(GS); (increased EOS)

**Asthma Cluster Analysis: 5 Clusters**

- 3 More Severe Older Onset Asthma**  
Older; Late onset(LOA); higher BMI; Less atopic; Moderately low FEV1 with some reversibility; Higher dos (CS); > 3 Controllers, but despite this more OCS bursts (increased sputum EOS)
- 5 Severe Fixed Airflow Asthma ("COPD similarities")**  
Older; (longest duration); 63% female; Less atopic; Severely decreased FEV1 less reversibility; On OCS; higher BMI; more GERD,HTN; High HCU, Beta use & GSS; (increased PMN, EOS)

**Relationship of Guideline Asthma Severity Classification and Cluster Assignment (Clusters 1-5)**



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

