Asthma

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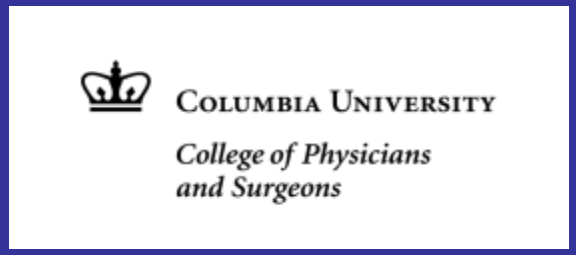
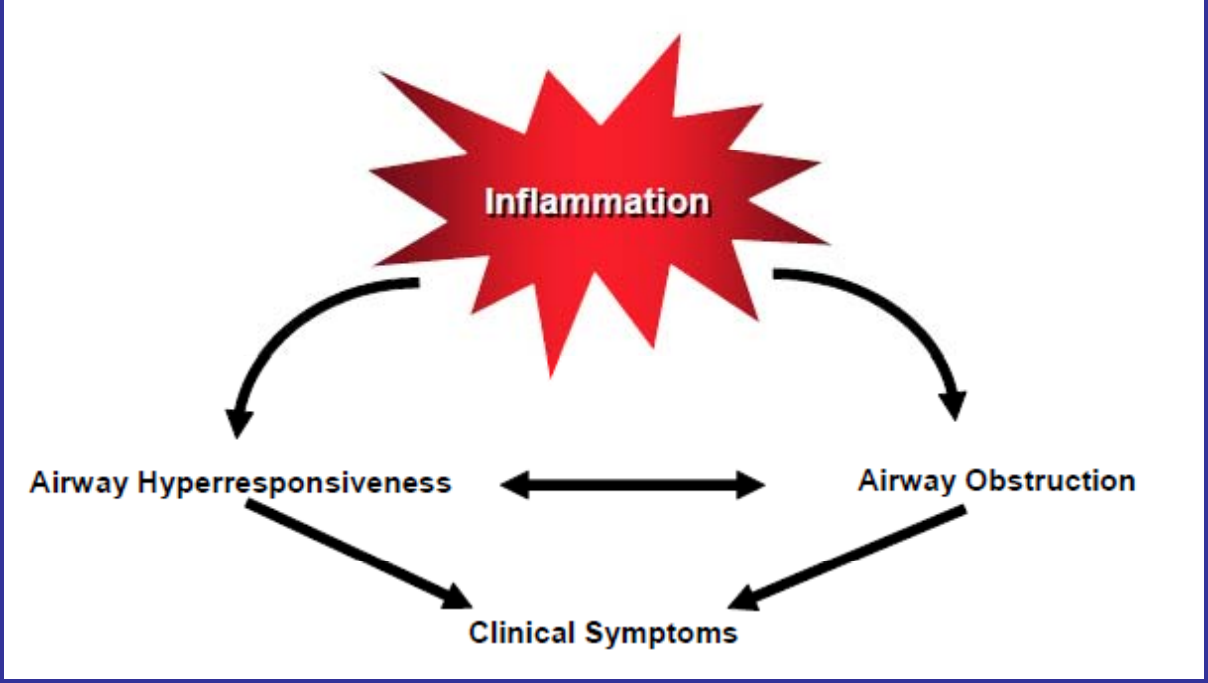
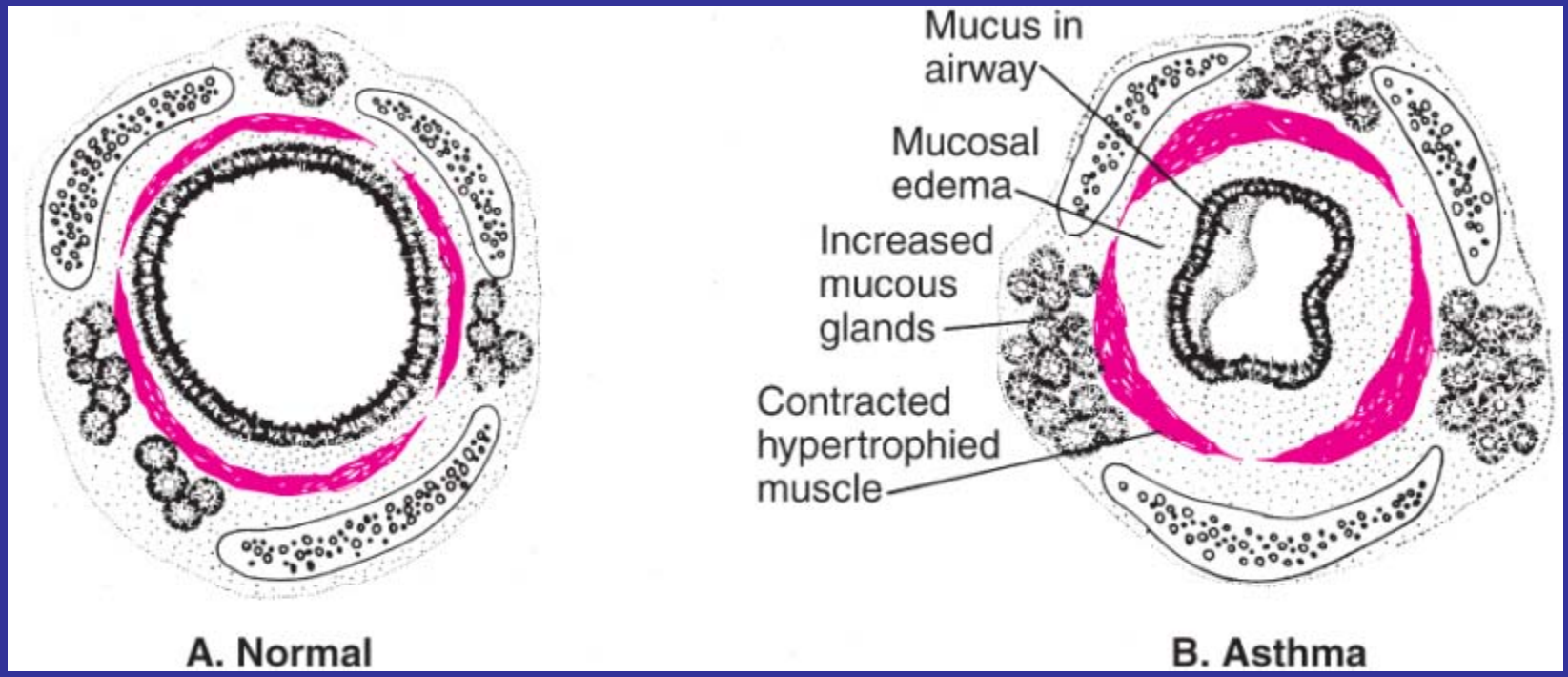


Asthma Definition

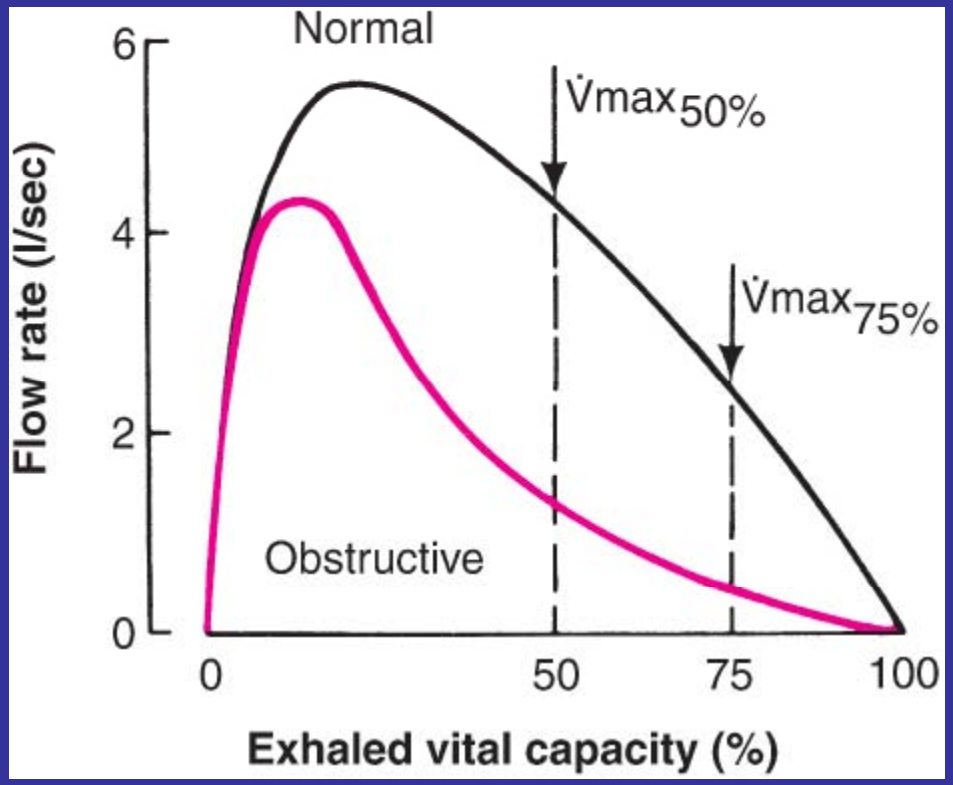
Asthma is a chronic inflammatory disorder of the airways characterized by airway hyperresponsiveness, airflow obstruction, and clinical symptoms.



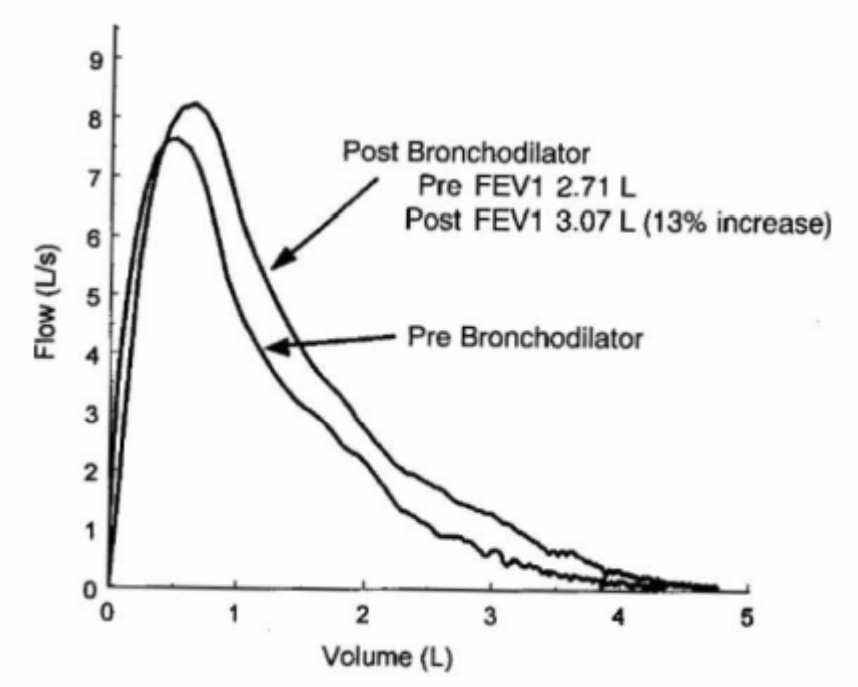
Bronchial Wall in Asthma



Flow volume loop: Airflow obstruction



Reversible Airflow Obstruction



- Improvement in FEV_1 and/or FVC after an inhaled bronchodilator
- 12% relative increase AND 200 ml increase is “significant”
- Smaller improvements may still be important

Bronchial Hyperresponsiveness

- Patient breathes in nebulized methacholine or histamine
- Both drugs provoke bronchoconstriction that can then be quantified by spirometry
- People with pre-existing airway hyperreactivity, such as asthmatics, will react to lower doses of drug
- decline in FEV1 of 20% from your baseline reading is considered a positive test.

Gas exchange in asthma

- Gas exchange is normal between attacks
- During attacks
  - V/Q mismatch causes hypoxemia
  - Typically mild
  - May be severe

Alveolar Ventilation in Asthma

- During an attack….
  - Alveolar hyperventilation nearly universal
    - Due to increased minute ventilation
- When severe…
  - Alveolar hypoventilation can occur
    - Due to respiratory muscle fatigue and increased dead space
    - Can be fatal!

Asthma symptoms

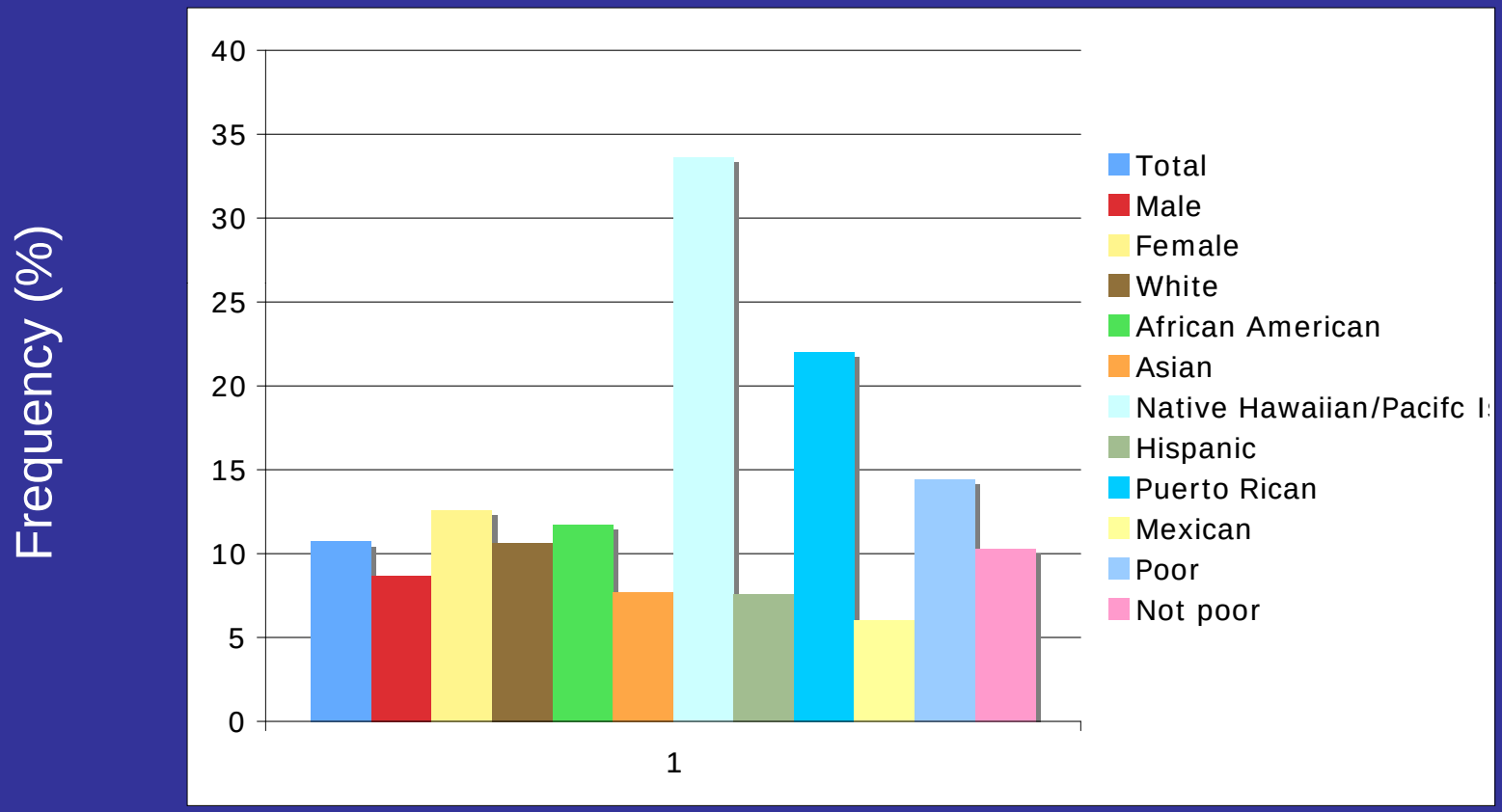
- Asthma is an episodic disease
- Between attacks
  - Symptoms vary depending on “asthma control”
  - Nocturnal symptoms are common
- During attacks
  - Wheeze
  - Cough
  - Chest tightness

Differential diagnosis of wheezing

- Upper airway obstruction
- Lower airway obstruction
  - Asthma
  - COPD
  - Cystic fibrosis & bronchiectasis
  - Large airway obstruction
    - Tumor, stenosis, foreign body aspiration, et al.
  - Bronchiolitis
  - Pulmonary edema
  - Carcinoid syndrome

Why learn about asthma?

Ever asthma diagnosis, US, 2005, adults*

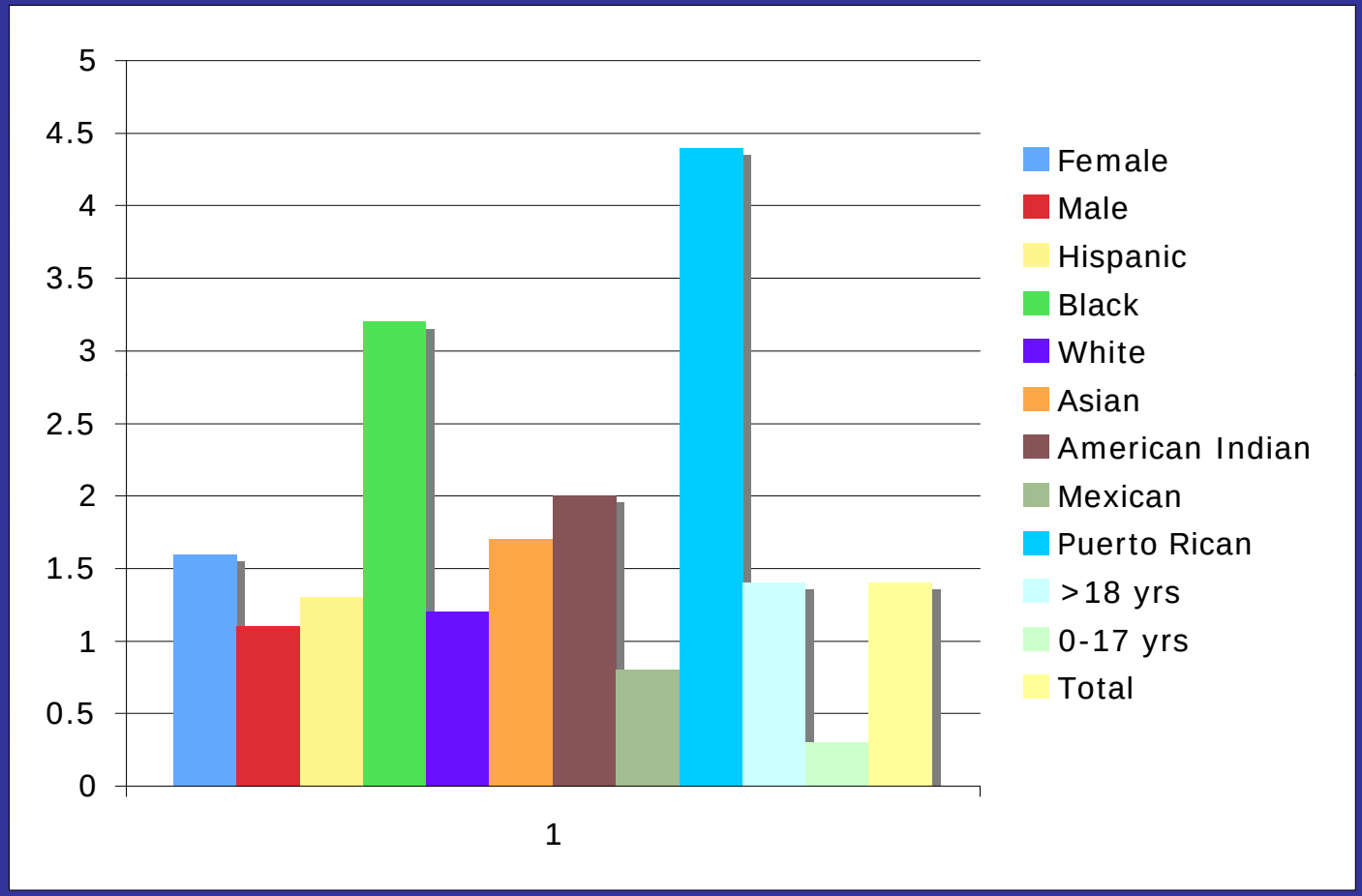


*23 million adults lifetime asthma diagnosis

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Asthma deaths, 2003*



Per 100,000 Population

*3780 asthma deaths 2004, or 1.3/100,000, or > 10 people/day

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Asthma Causes and Triggers

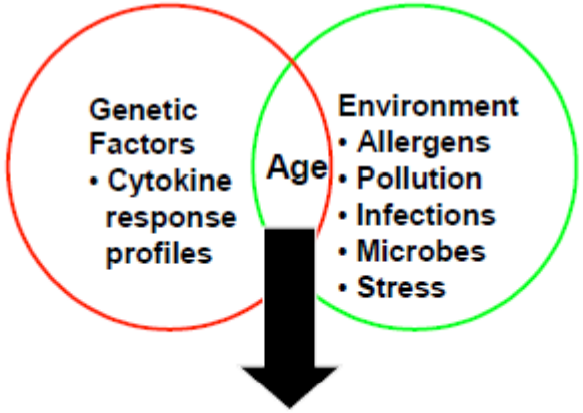
Causes of Asthma

- Genetic and/or epigenetic predisposition;
  - FCεR1, CD14, IL-4, IFNγ, B2AR; ACSL3*
- Environment
  - allergic sensitization, fewer sibs, excessive hygiene, prenatal antibiotic exposure, vaccination, farm
- Prenatal exposures
  - Parent of origin effect for IgE, asthma; maternal parity; maternal smoking
- Prenatal diet
  - Increased methyl donors; reduced zinc, vitamin E, vitamin D, zinc; Mediterranean diet

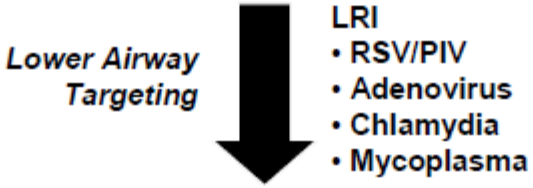
* Studied at Columbia

Chung, Miller, et.al. *Arch. Dis. in Child. Fetal Neonatal Ed*. 92: 68-73, 2007.
R. Miller, *JCI*, 118(10):3265-3268 2008.

Pathogenesis of Asthma



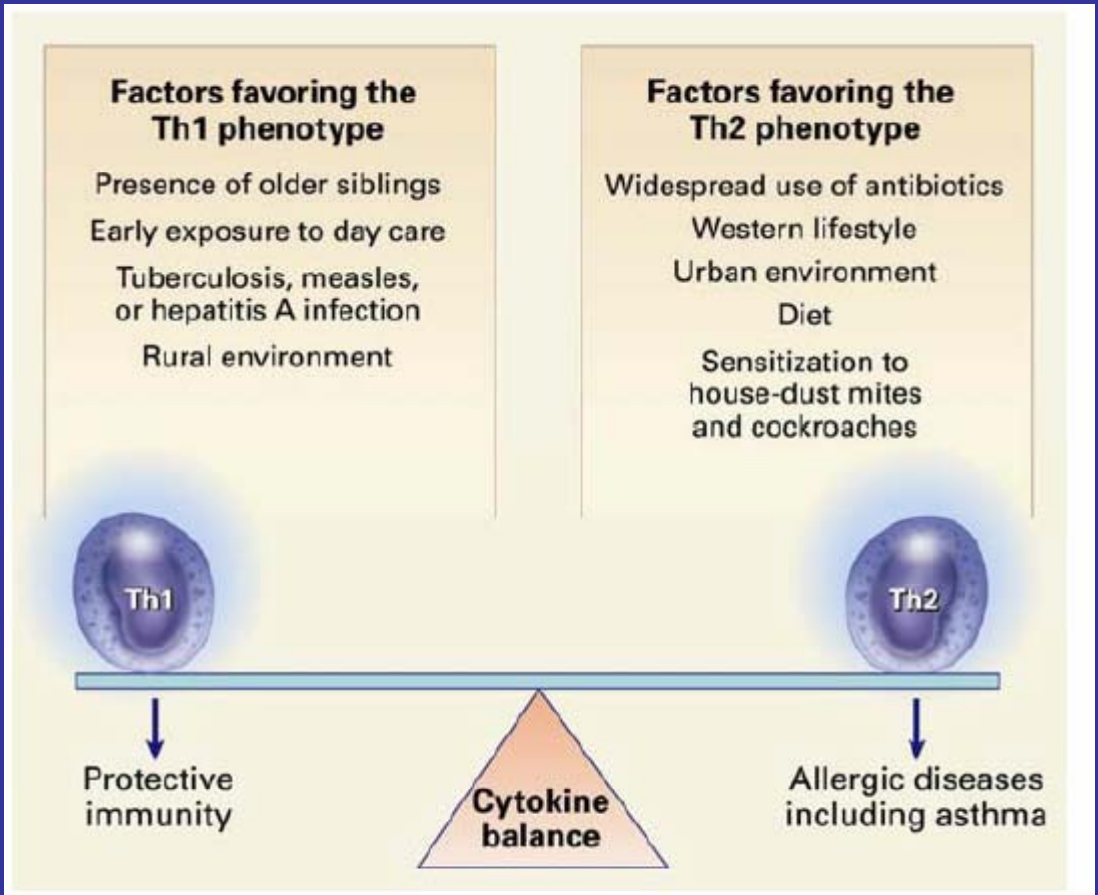
Altered Innate and Adaptive Immune Responses



Persistent wheezing and asthma

Key: LRI, lower respiratory illnesses; RSV, respiratory syncytial virus; PIV, parainfluenza virus

Cytokine Balance



Hygiene hypothesis

Increased cleanliness in 20th century Western Society has led to greater number of allergic (Th2 skewed) individuals.

Protective exposures offered as evidence of the 'Hygiene hypothesis'

- Older siblings — Strachan, BMJ 1989
- Lack of vaccination — Shirakawa, Science 1997
- Early life respiratory infections — von Mutius, E Resp J 1999
- Parasitic infection — Yazdanbaksh, Lancet 2000, Science 2004
- Day care attendance — Ball, NEJM 2000
- Gut microflora — Kalliomaki, Lancet 2001
- Animal exposure — Platts-Mills, Lancet 2001
- Consumption of unpasteurized milk — Riedler, Lancet 2001
- Exposure to a barn in the 1st year of life — Riedler, Lancet 2001
- Bacterial endotoxin — Braun Fahrlander, NEJM 2002

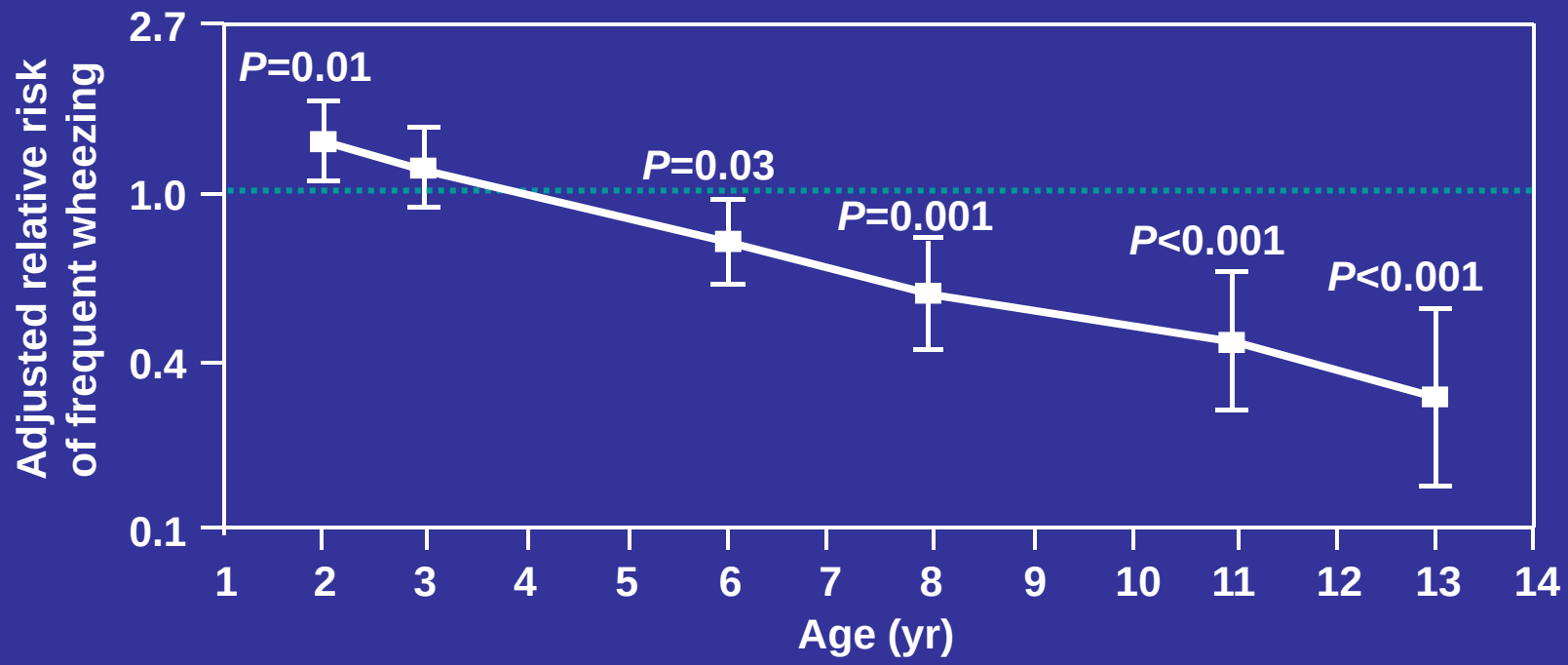
Protective effect of respiratory infections in infancy

- ≥2 episodes of “common cold” before age 1 yr decrease risk of asthma by age 7 by ~50%
- Other viral infections also protective
  - herpes
  - varicella
  - measles
- LRI with wheeze in the first 3 years of life increases risk of asthma

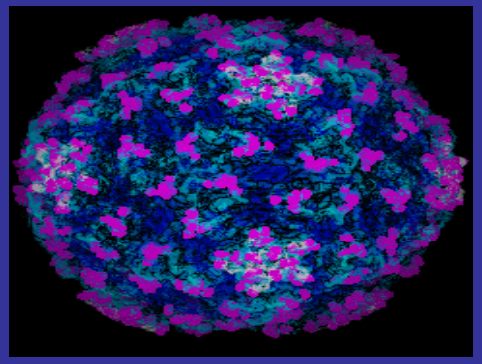
Illi S et al. *BMJ*. 322:390, 2001

Protective effect of early day care and older siblings

Children who had ≥2 older siblings or attended day care during first 6 mo of life had increased risk of wheeze early in life but decreased risk later.



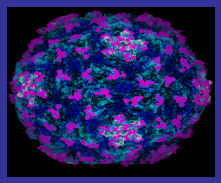
Asthma triggers



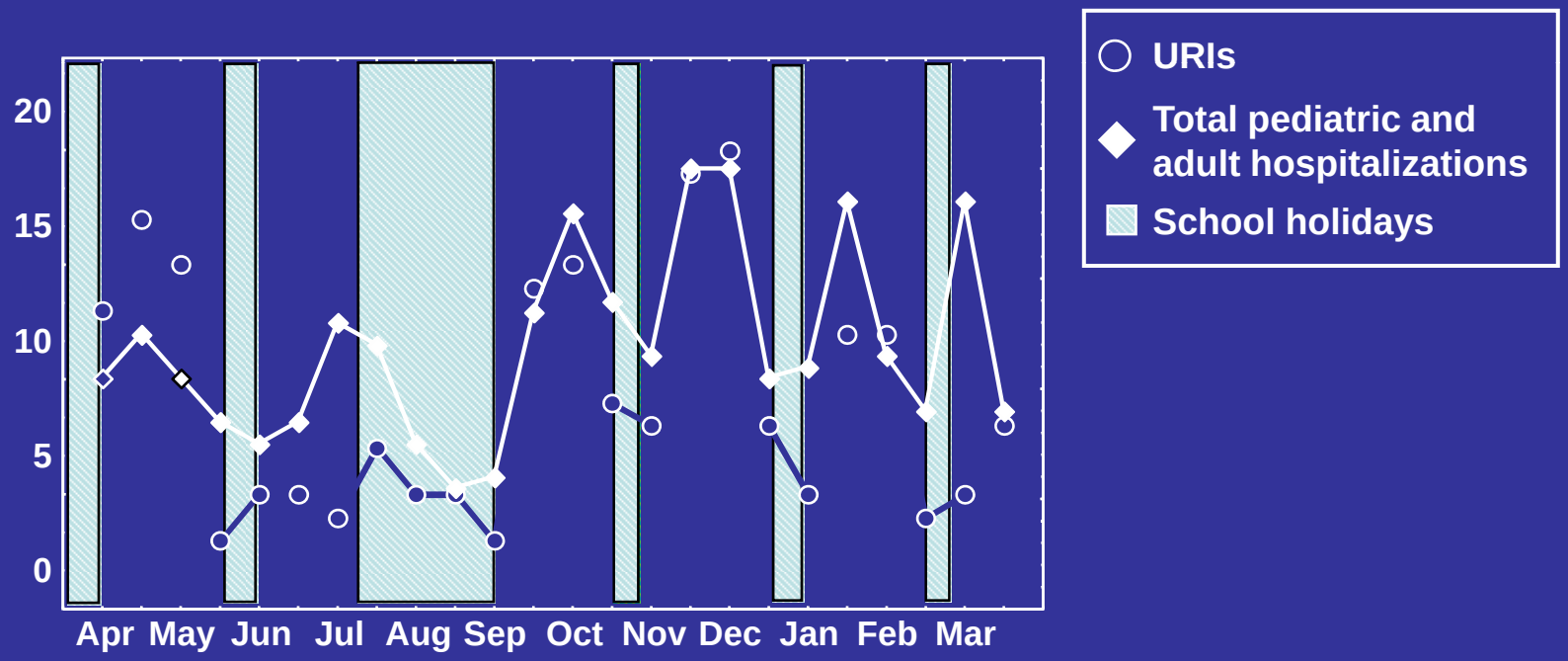
Allergens

- Small proteins (2-60 microns)
- Highly soluble
- Inhaled in dessicated particles (pollen grains, mite feces)
  - easily elute from the particle
  - diffuse into respiratory mucosa
- Enzymatically active (eg. proteases)
- Seasonal patterns of pollination:
  - Spring-trees
  - Summer-grass
  - Fall-ragweed

Viruses



Hospital admissions correlate with virus isolation peaks and school terms

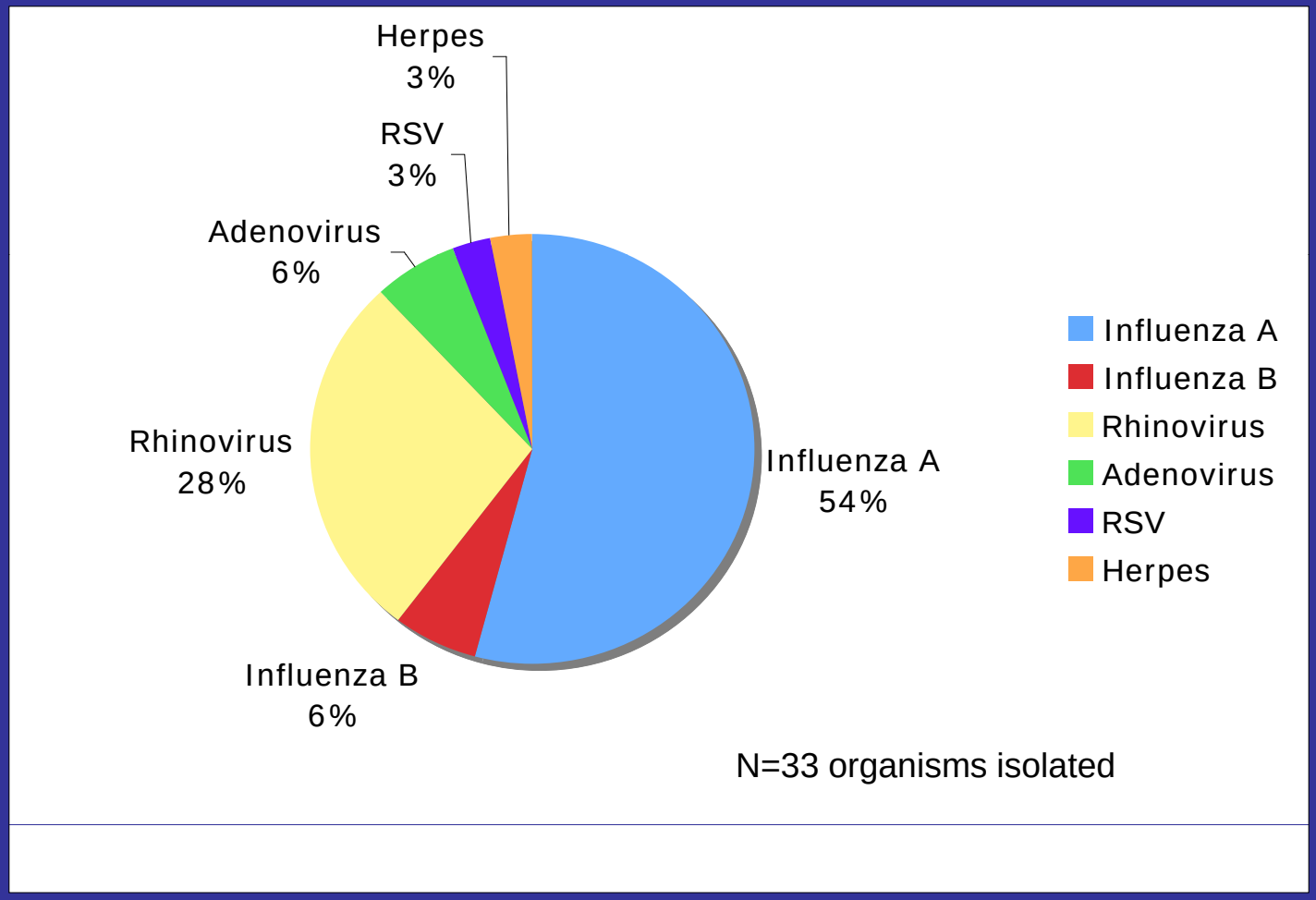


Johnston et al. *AJRCCM.* 154:654, 1996

Johnston et. al. *BMJ*. 310:1225-1229, 1995

Nicholson et al. *BMJ*.;307:982, 1993

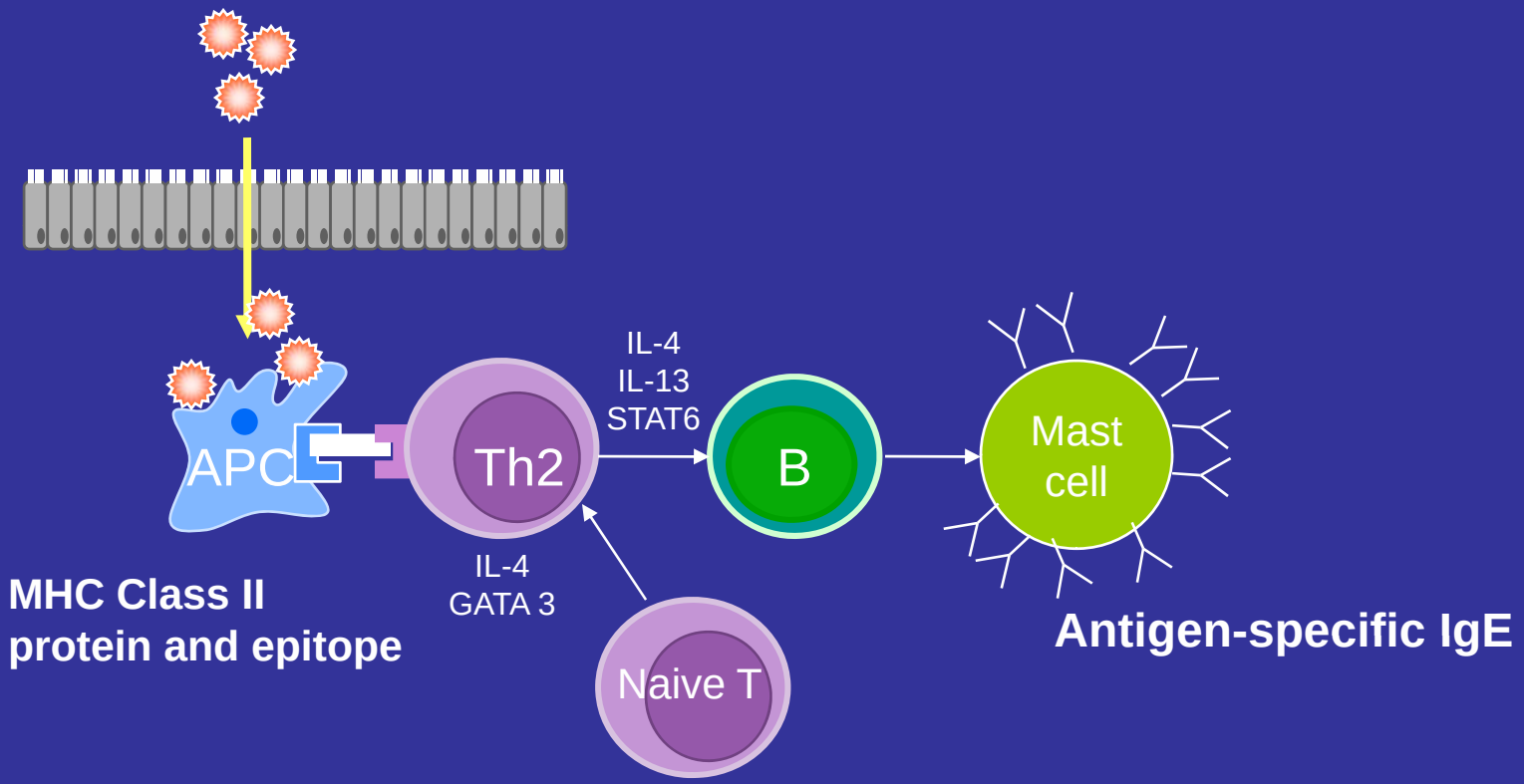
Viruses detected in adults hospitalized with asthma



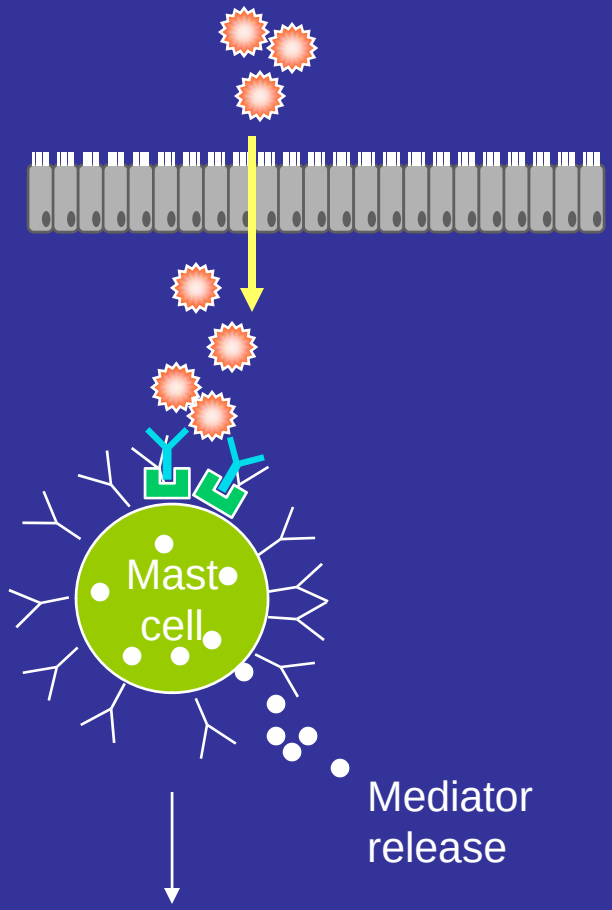
Teichtahl H et al. *Chest*.112:591, 1997

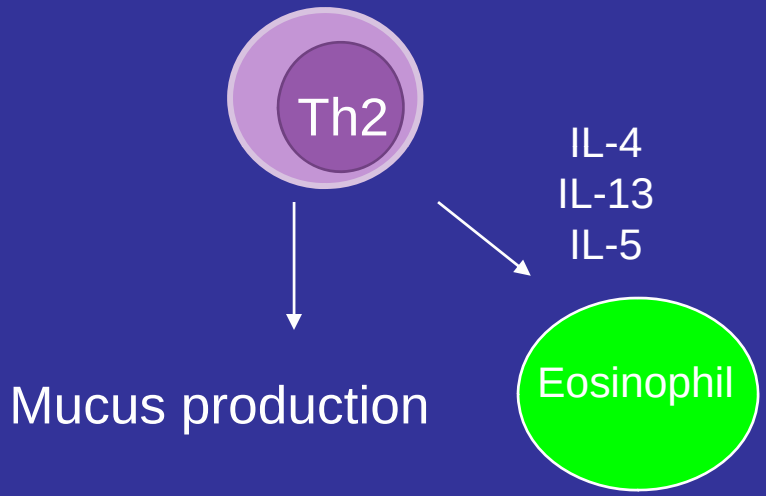
Immunopathogenesis

Immunological mechanisms: Allergic sensitization



Immunological mechanisms: Reexposure

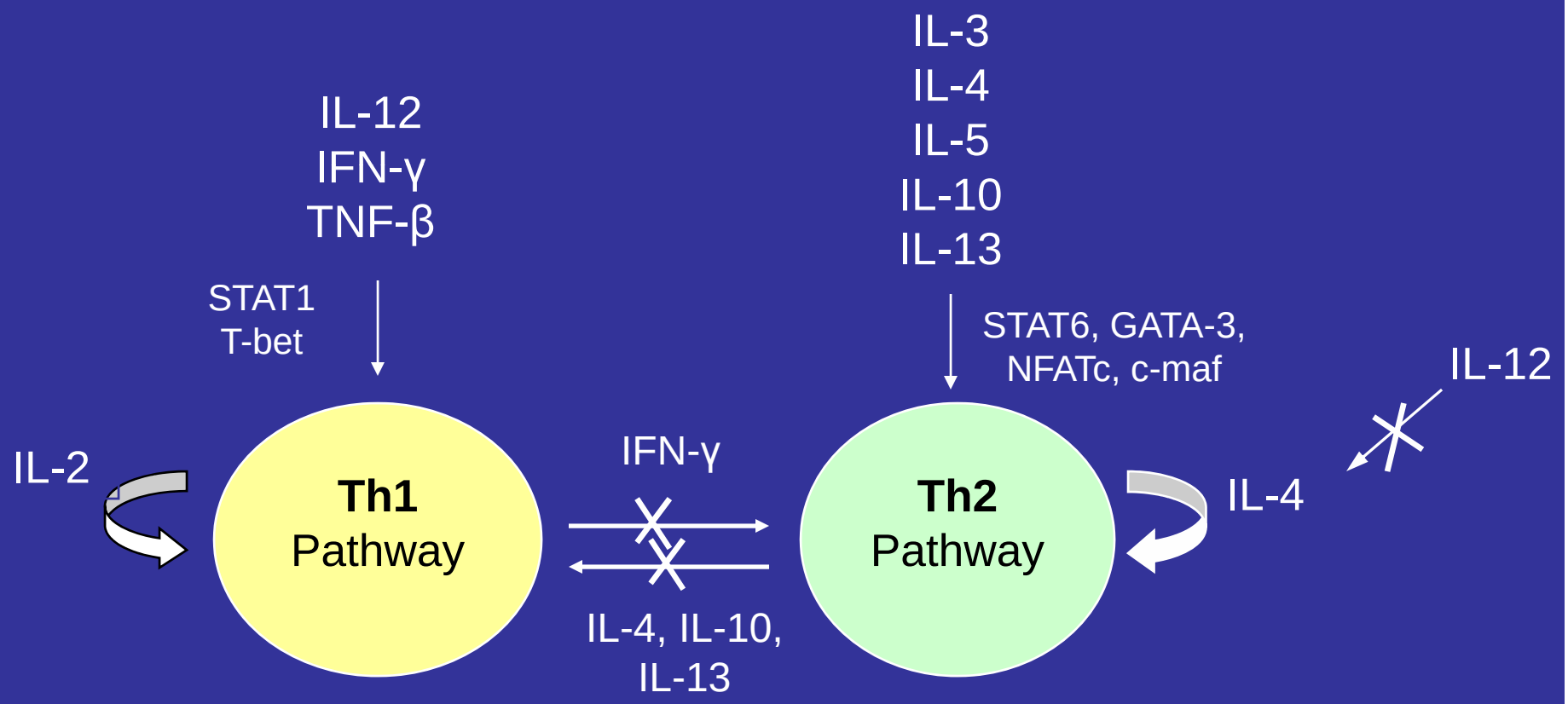




Immediate reaction

Late phase reaction

Counter-regulatory actions of the Th1 and Th2 pathways



IgE-dependent release of inflammatory mediators

- Immediate: Granule contents
  - Histamine
  - TNF-α
  - Proteases
  - Heparin
- Over minutes: Lipid mediators
  - Prostaglandins
  - Leukotrienes
- Over hours: Cytokine production
  - IL-4
  - IL-13

Biomarkers

- IgE
- eNO
- Sputum eosinophilia
- Chitinase-like proteins

Chupp et al *N Engl J Med.* 2007;357(20):2016-27

Asthma Subgroups

Occupational asthma

- "Variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors or fumes"

- Two types
  - Specific IgE-mediated
  - Irritant induced (RADS)

Etiologies of occupational asthma: Low molecular weight chemicals

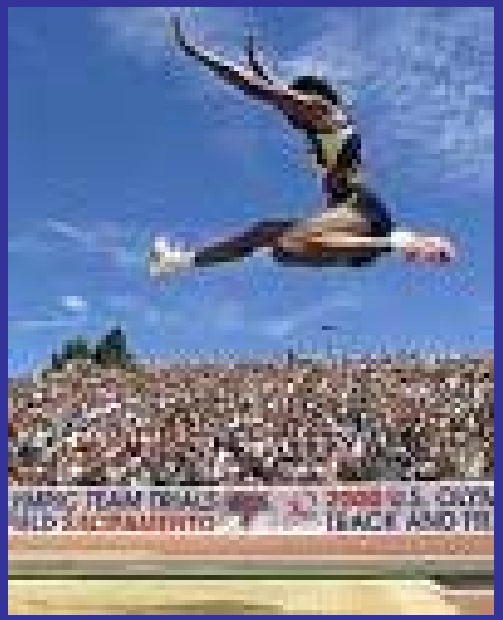
- Isocyanates (HDI, MDI, TDI)
- Woods (red cedar, exotic, sawmills)
- Glues (methacrylates, cyanoacrylates)
- Epoxies (anhydrides, amines)
- Colophony
- Dyes

Etiologies of occupational asthma
High molecular weight chemicals

- Flour - cereals
- Animal handling (dander)
- Latex
- Psyllium
- Crab processing
- Enzymes (eg. papain as meat tenderizer)

Exercise-induced asthma

Olympic gold medalists with asthma



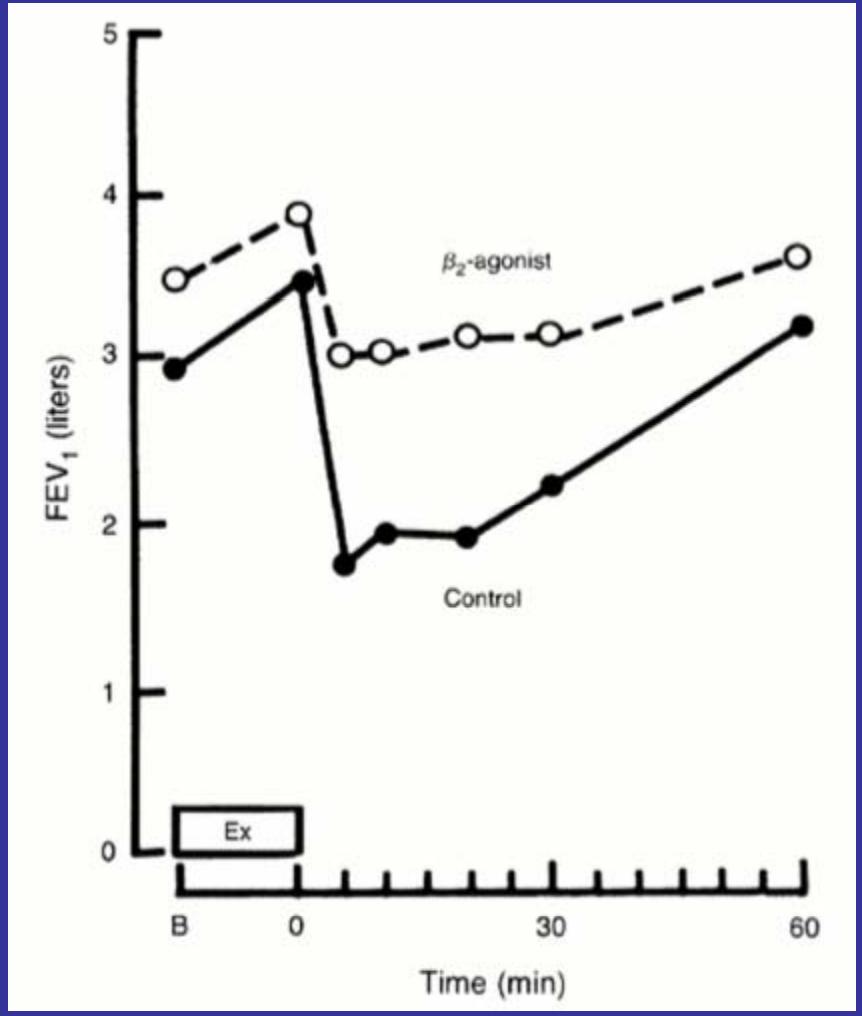
And the entire 1988 U.S. water-polo team

DT, JJK, AS, TD

Exercise-induced asthma (EIA): Defn

- Self-limited syndrome of cough and/or wheezing, chest pain or chest tightness developing within 30 minutes of 2-8 minutes of continuous exercise or afterwards.
- Often reflection of the underlying asthma condition

Changes in pulmonary mechanics during and after exercise



McFadden, ER, et al. *New England Journal Medicine* (19):1632-7.1994

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Pathogenesis

- Thermal hypothesis
  - cold air → ↑ blood flow to bronchial circulation → airway obstruction
- Osmotic hypothesis
  - cold dry air → in loss of fluid from the airway → hyperosmotic state → mast cell degranulation → releases bronchoconstrictive mediators → increases bronchovascular permeability

McFadden, ER. *Allergy Principals and Practice* (66):953-962. 1998
Anderson, SD. *JACI* 105:453-9.2000

Sports specific factors

- Skaters: Ice resurfacing machines-emit PM’s
- Swimmers: inhaled chlorine (that produces nitrogen trichloride) can cause airway inflammation and lung epithelial hyperpermeability

Rundell. *Inhal Toxicol* 15(3): 237-50, 2003.

Refractory Asthma: Types

- Severe despite appropriate therapy, vs
- Under-treated because of adherence or other problems
- “brittle” vs. nonbrittle

Airway remodeling

- Inflammation
- Mucus hypersecretion
- Subepithelial fibrosis
- Airway smooth muscle hypertrophy
- Angiogenesis

Refractory asthma: differential diagnosis

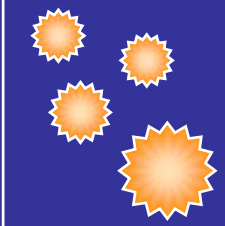
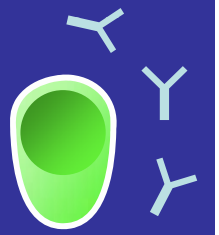
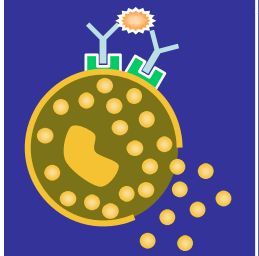
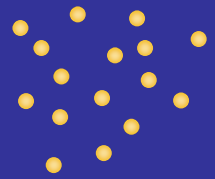
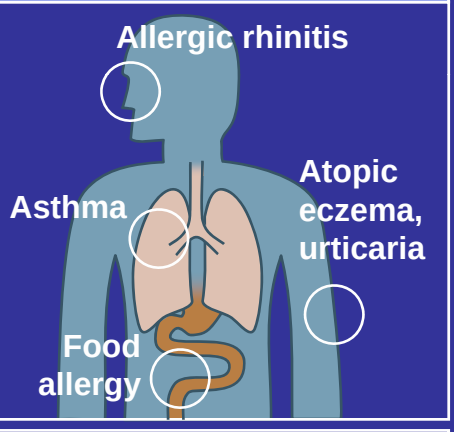
- Mild asthma with another functional breathing problem
- Stridor
- Persistent isolated cough
- Prolonged wheezing from bronchiolitis (infants)
- COPD
- LV Dysfunction
- VC Dysfunction (32% coexistent asthma)

Status asthmaticus

- An attack that continues for hours or even days without remission despite bronchodilator therapy
- Can be life-threatening
- May require mechanical ventilation

Asthma Management

Targeted treatment of asthma

	Allergen	IgE synthesis	Mast cell degran-ulation	Inflammatory mediators	Clinical symptoms
Mechanism					
Treatment	Allergen avoidance	Hypo-sensitization	Mast-cell stabilization: cromones, Isoprenaline Omalizumab	Mediator antagonists: antihistamines, antileukotrienes	Late-phase inhibitors: steroids

Adapted from Roitt J. Essential Immunology. 1994.

NAEPP Classification of Asthma Severity

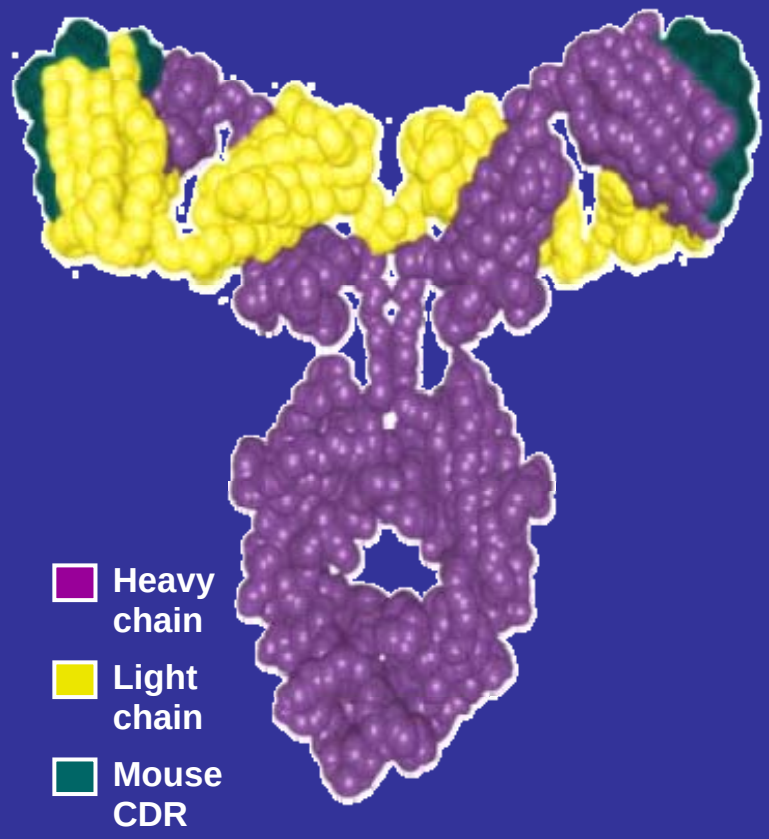
	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Symptoms (days/week)	≤2	>2	Daily	Throughout the day
Nighttime awakenings (times per month)	≤ 2	3-4	>4	Often 7x/week
FEV_1	Normal	>80% predicted	60 to 80%	<60%
Initial Treatment Step	Step 1	Step 2	Step 3	Step 4 or 5

Updated 2007 NAEPP guidelines: 6 steps

- Step 1 - short acting inhaled beta agonist prn
- Step 2 - Low dose inhaled corticosteroid (ICS)
- Step 3 - Medium dose ICS or low dose ICS plus inhaled long acting beta agonist (LABA)
- Step 4 - Medium dose ICS plus LABA
- Step 5 - High dose ICS plus LABA
  - consider omalizumab (anti-IgE) therapy
- Step 6 - Oral corticosteroid

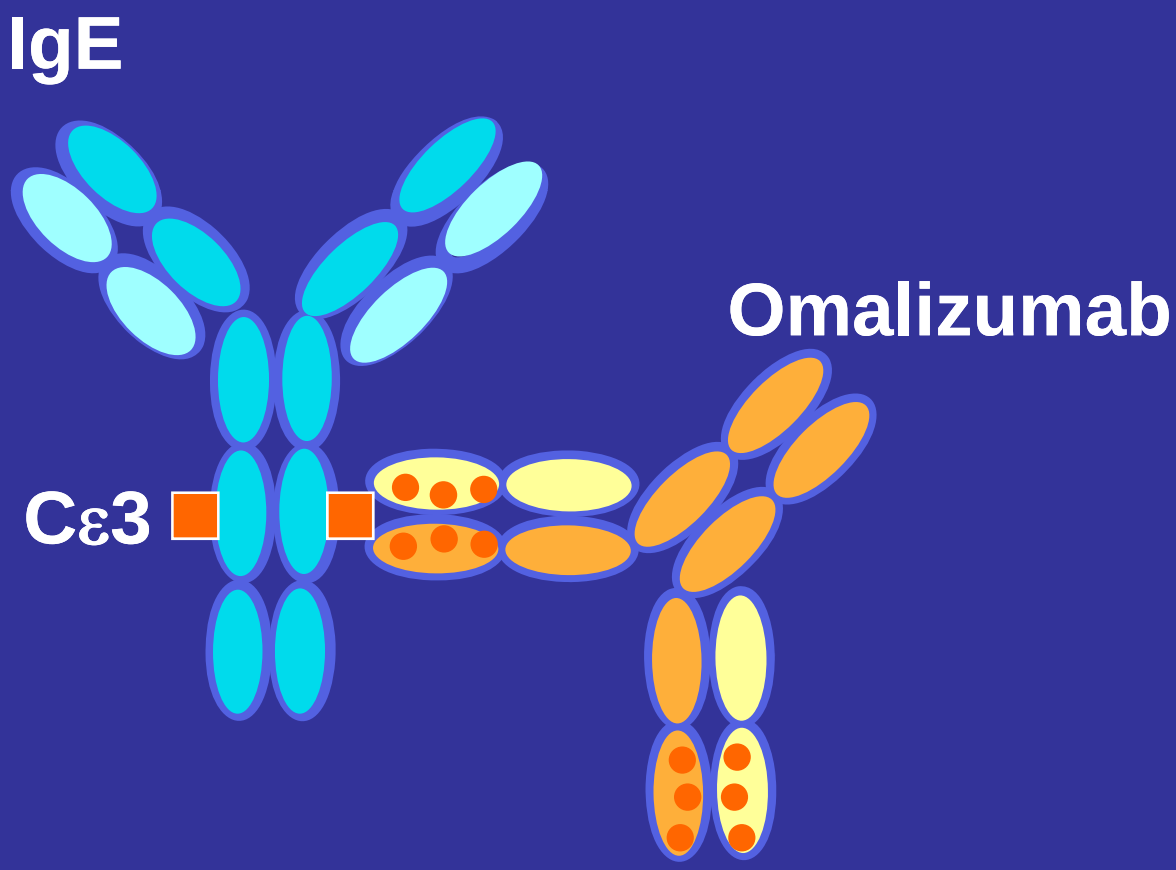
Omalizumab

- IgG1 kappa human framework containing murine antibody complementarity-determining regions (CDRs) (MW 150 kd)
- Humanized mAb against IgE (95% human)
- Binds circulating IgE regardless of specificity
- Does not activate complement
- Forms small, biologically inert omalizumab:IgE complexes

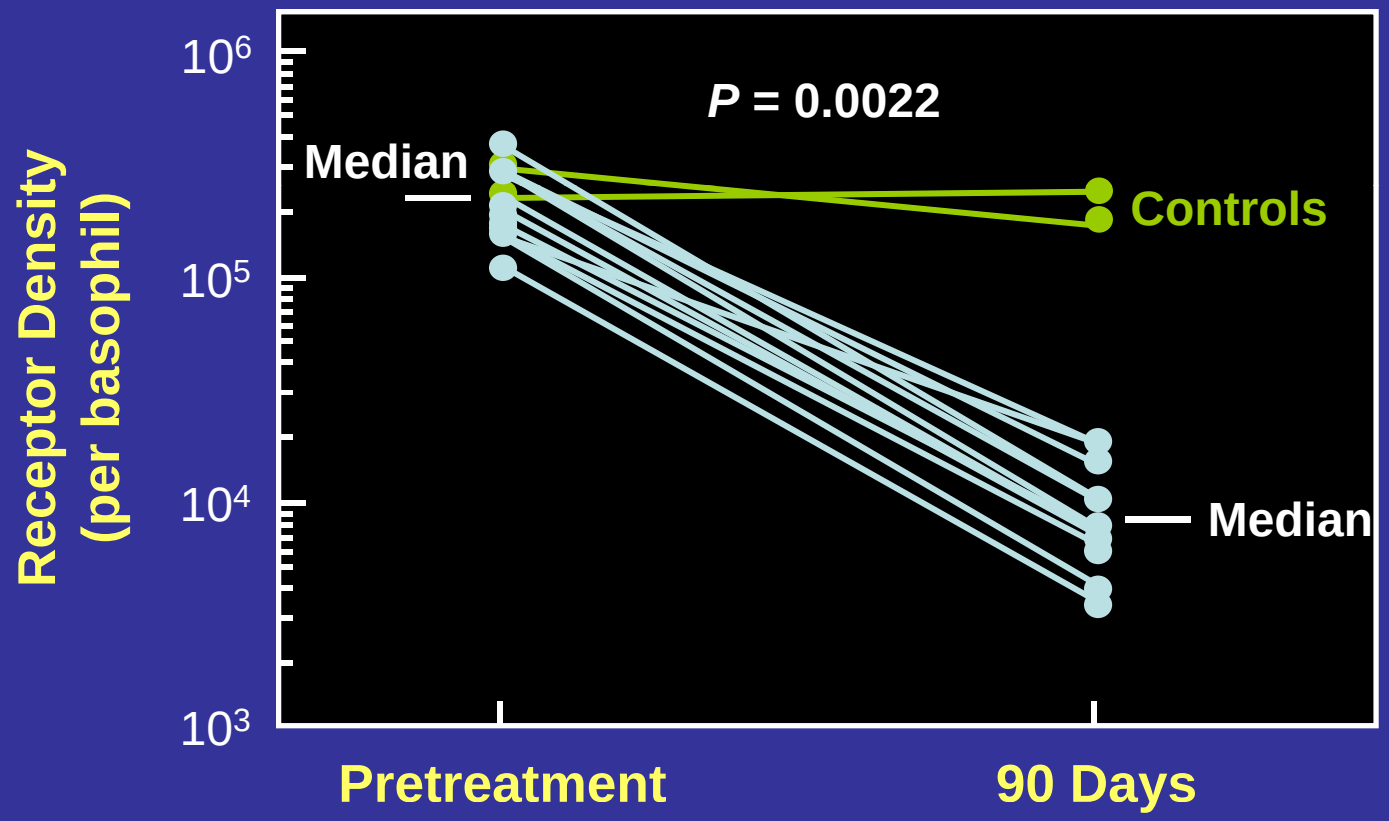


Adapted from Boushey H. *J Allergy Clin Immunol.* 2001;108:S77-S83

Omalizumab complexes bind free IgE and interrupts allergic cascade



IgE receptors downregulated



MacGlashan D, et al. J Immunol. 1997.

High-risk patients

- Significant add-on therapy
  - Halves the number of asthma exacerbations
  - Reduces the likelihood of re-hospitalization
- Consistent reduction in exacerbation rates across all FEV_1 severity groups
- Greater improvements in lung function, asthma symptoms, and asthma-specific quality of life

Asthma Meds Under Scrutiny

- Pursuant to the 1987 Montreal Protocol, CFC propelled MDI off the marked and replaced with HFA ($, better?)
- 12/08: Large FDA hearing on the safety of LABAs:
  - SMART trial: increases in asthma-related deaths and life-threatening experiences in subjects treated with salmeterol vs placebo.
  - No requirement for concurrent treatment with inhaled ICS
  - supports the safety of LABAs when used with ICS
- 3/08; 1/09: FDA early communication about an ongoing safety review of montelukast in response to a possible association with behavior/mood changes, suicidality; incidence of suicidal ideation was less than 0.01%; no FDA conclusion yet
- 10/08: FDA early communication about increased risk for cardiovascular events in patients who received inhaled anticholinergic drugs (Tio); studies confounded by design; new update expected soon