Allergy and Asthma

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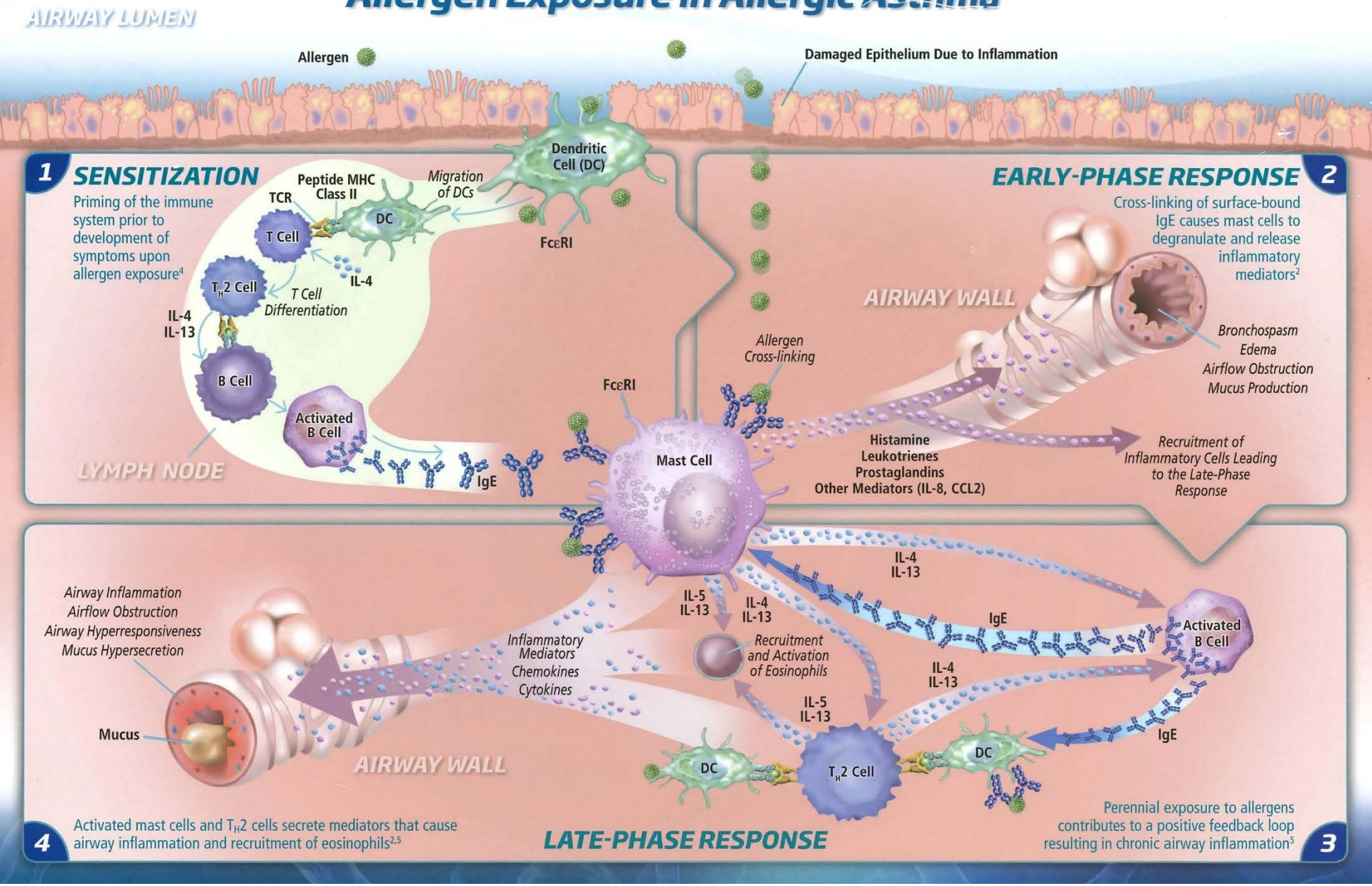
The Role of the Mast Cell in Chronic Inflammation Due to Allergen Exposure in Allergic Asthma[1-3,*]



Objectives

- **Characterize asthma based on phenotypes**
- **Define how atopy influences asthma development in children and adults**
- **Define diagnostic options to define IgE mediated influences on asthma**
- **Consider immunotherapy to modify outcomes in IgE mediated asthma**
- **Utilize phenotypes in defining best treatment options for patients with moderate to severe persistent asthma**

Defining Asthma by Phenotypes

- **Phenotype – expression of genotype as influenced by environment – clusters of characteristics used to define asthma**
- **Review of pubmed.gov reveals numerous articles adding "phenotypes" to the reasons for asthma – ever expanding playing field**
- **NHLBI multi-organization collaboration in 2011 defined the following phenotypes**
  - **One size does not fit all – interrelate**

Asthma Phenotypes

- Define 9 phenotypes in 3 general categories:

- Trigger-induced asthma

    1. Allergic
    2. Non-allergic
    3. Aspirin-exacerbated respiratory disease (AERD)
    4. Infection
    5. Exercise-induced

Asthma Phenotypes

- Clinical presentation of asthma
    6. Pre-asthma wheezing in infants
        - Episodic (viral) wheeze
        - Multi-trigger wheezing
    1. Exacerbation-prone asthma
    2. Asthma associated with apparent irreversible airflow limitation
- Inflammatory markers of asthma
    1. Eosinophilic and neutrophilic asthma

Atopy and the Allergic Response in Asthmatics

What is “Atopy”

- **Essentially, atopy defines the tendency for a person to develop allergic (IgE mediated) disease**
- **IgE is the main culprit in provoking allergic or Type 2 mediated asthma and rhinitis**
- **IgE is made from B lymphocytes that are instructed by Type 2 converted T lymphocytes to produce IgE specific for one allergen**

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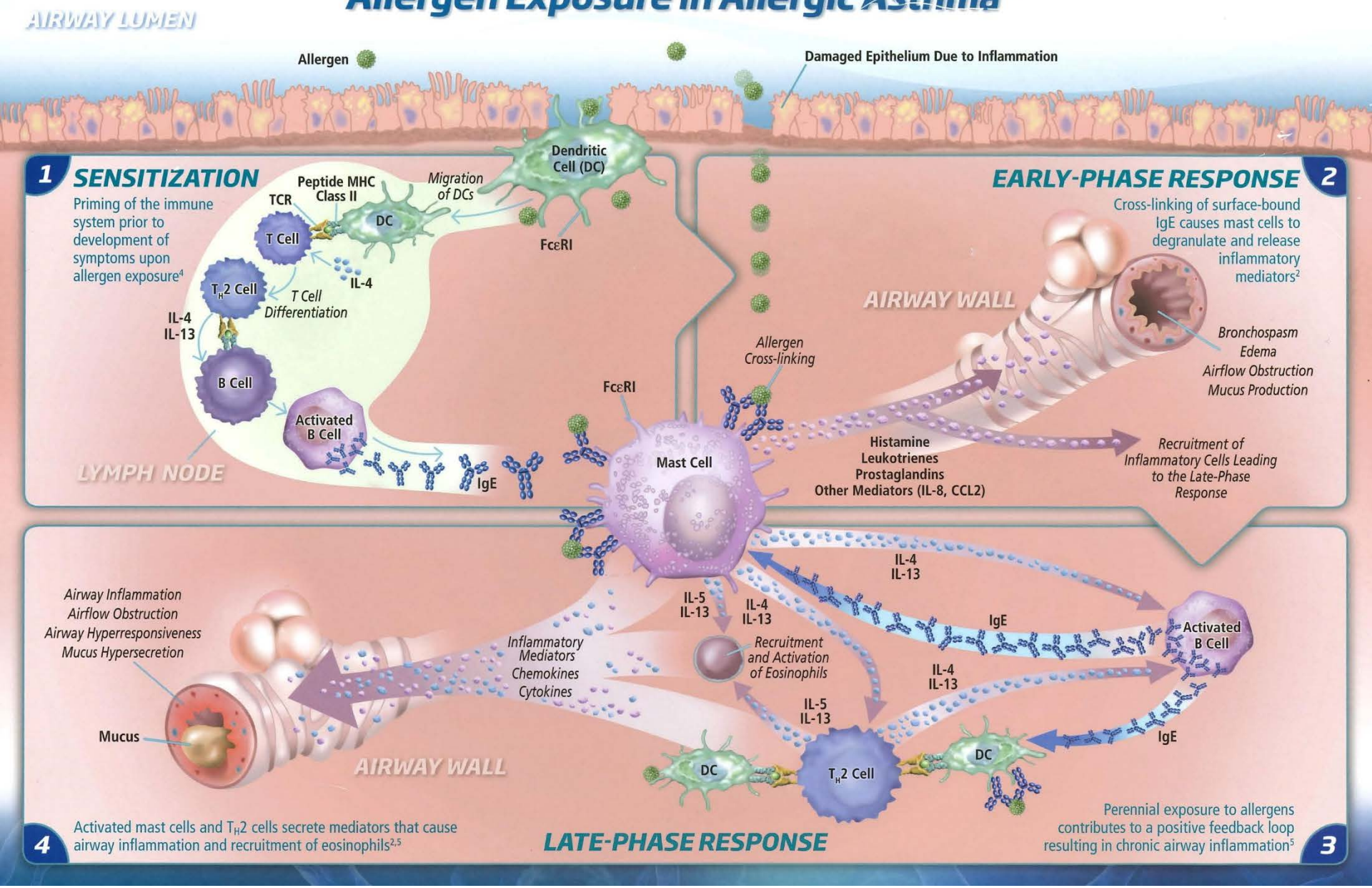
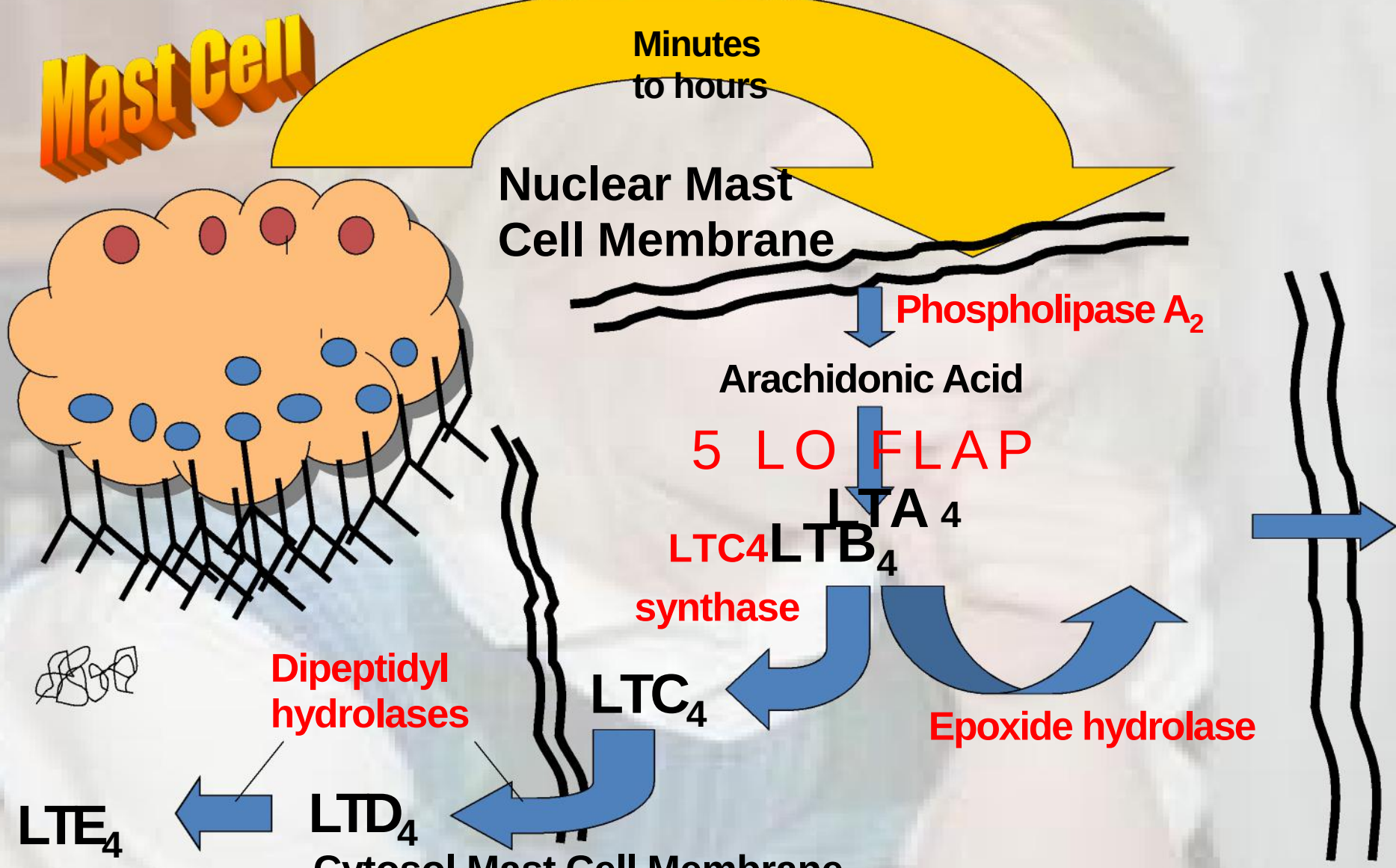


What Happens with IgE

- **Each mast cell is covered with thousands of IgE molecules – most specific for different allergens**
- **Cross-linking by an allergen of two adjacent IgE molecules "fires" the mast cell to release its inflammatory mediators**
- **Mediators such as LTD_4 are chemotactic for eosinophils and LTB are chemotactic for neutrophils**

Leukotriene Production in Allergy



The Result

- **Histamine and leukotrienes provoke bronchospasm and eosinophil chemotaxis**
- **Mast cell mediators IL4 and IL13 provoke perpetuation of the allergic response**
- **Eosinophil derived toxins cause breakdown of columnar epithelial layers**
- **Mucus hypersecretion from goblet cells add to the mess and blockage of airways**
- **Inevitable scarring of inner airways leads to changes in inflammatory cell mix with steroid resistant neutrophils**

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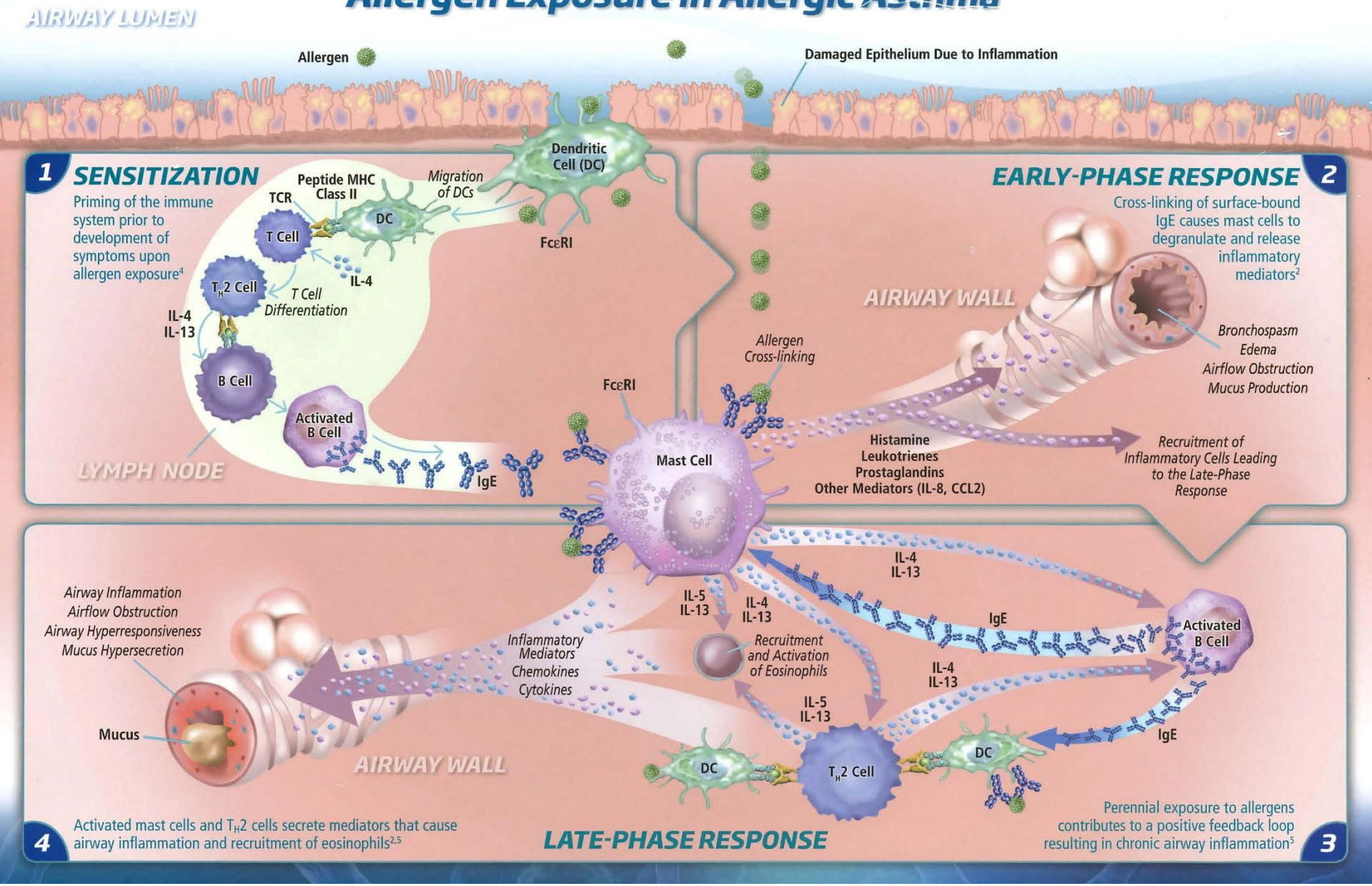


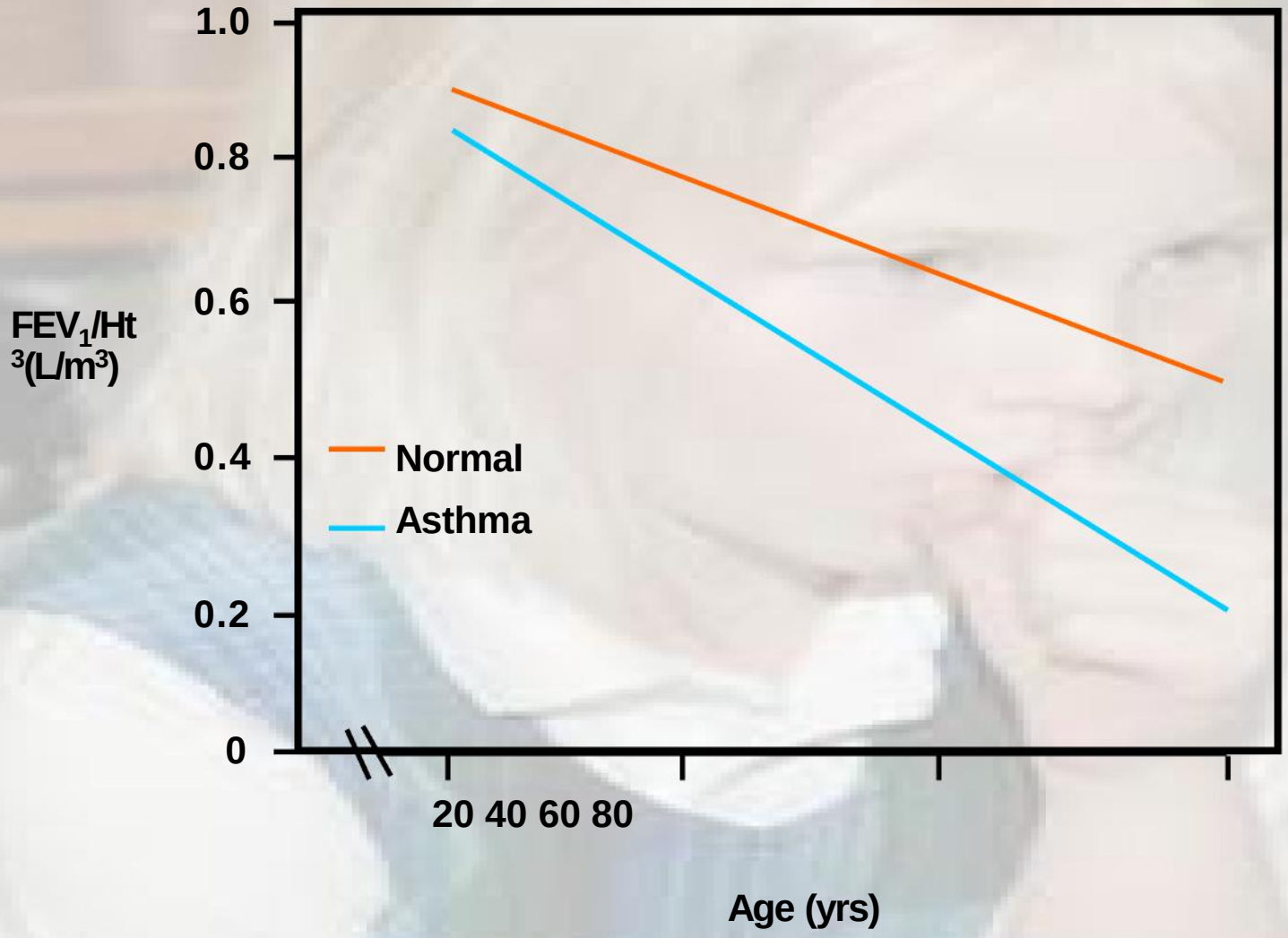
Theoretically ...

- **Prescribing a medication to suppress the allergic response should quell the reaction**

It's Not That Easy

- **The allergic response begins in early childhood for most children who develop asthma**
- **Those children grow into adults with asthma remissions occur during adolescence but you don't "outgrow your immune response"**
- **Must start early to modify the immune response**

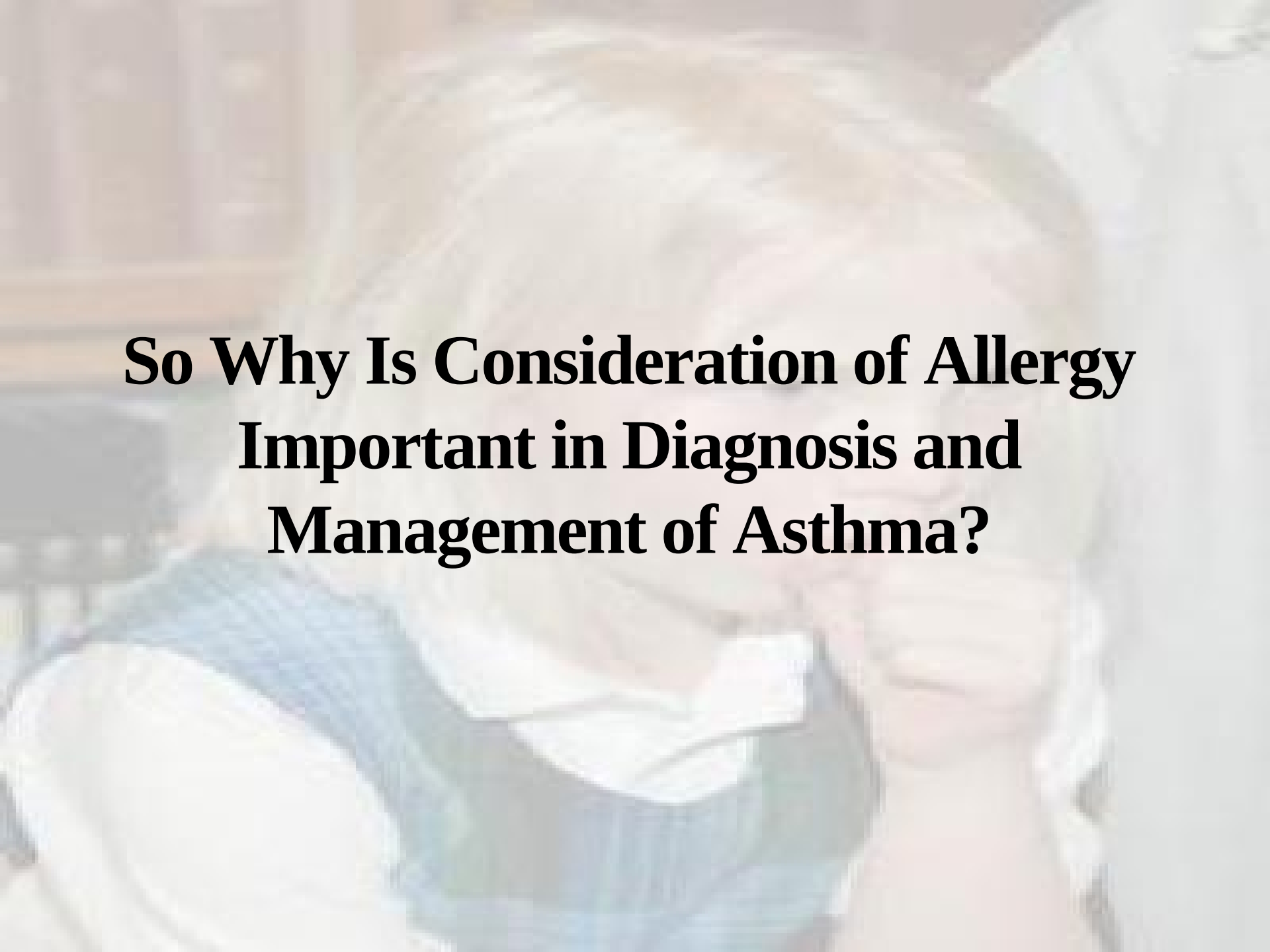
Rate of Decline in FEV_1



Adapted from Peat. *Eur J Respir Dis*. 1987; 70:171-179.

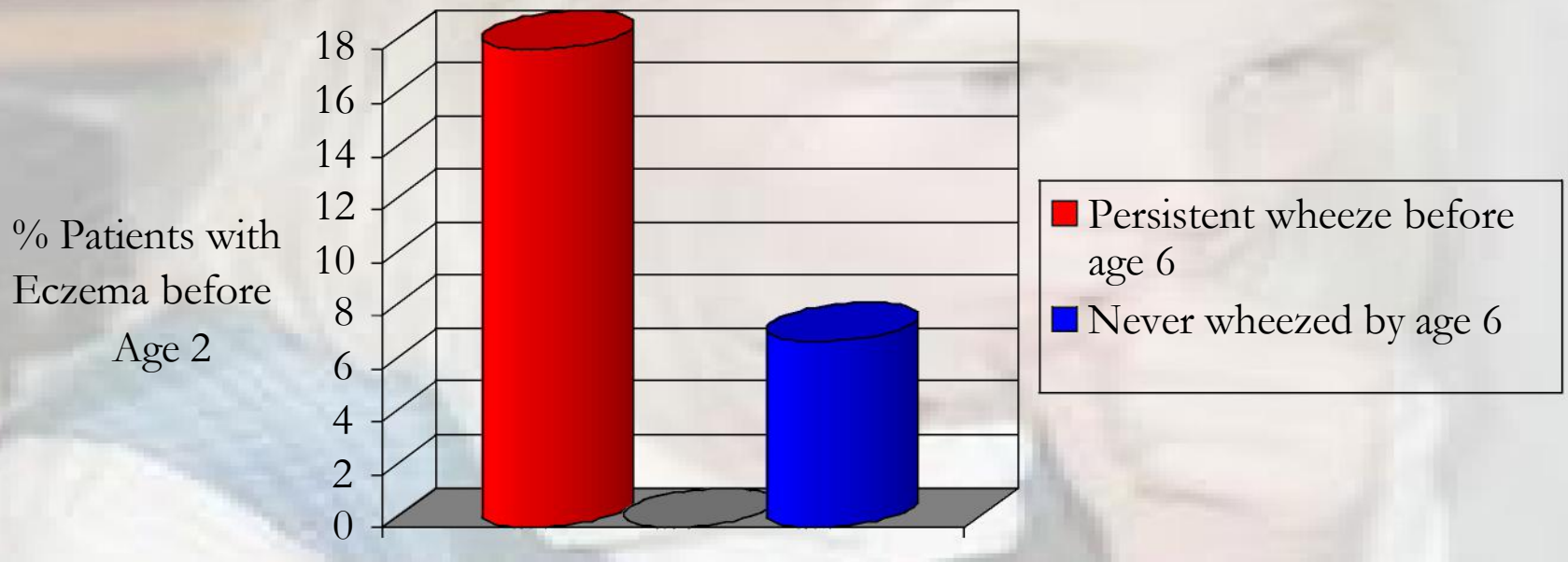
Has Any Therapy Reduced the Decline in Airflow with Time?

- **Allergen Immunotherapy?**
  When to start? Can immunotherapy be started for infants at risk?
- **Chemotherapy?**
  - **Prednisone, inhaled corticosteroids, muscarinic antagonists, LTRAs?**
- **Monoclonal antibodies?**
  - **Too soon to tell but not likely**
  - **$$$$$**



So Why Is Consideration of Allergy Important in Diagnosis and Management of Asthma?

Risk of Asthma in Those with Atopy



Martinez F, *et al. N Engl J Med* 1995; 332: 133-38

Asthma Predictive Index

History of greater than 4 wheezing episodes in one year (one - physician documented) PLUS

- **One major criteria:**
  - **Parent with asthma**
  - **Atopic dermatitis**

OR

- **Two minor criteria:**
  - **Food sensitivity (milk, egg or peanuts)**

If +, then 65% likelihood of developing asthma
If -, then 95% likelihood of NOT developing asthma

Importance of Identifying Sensitivities to Aeroallergens

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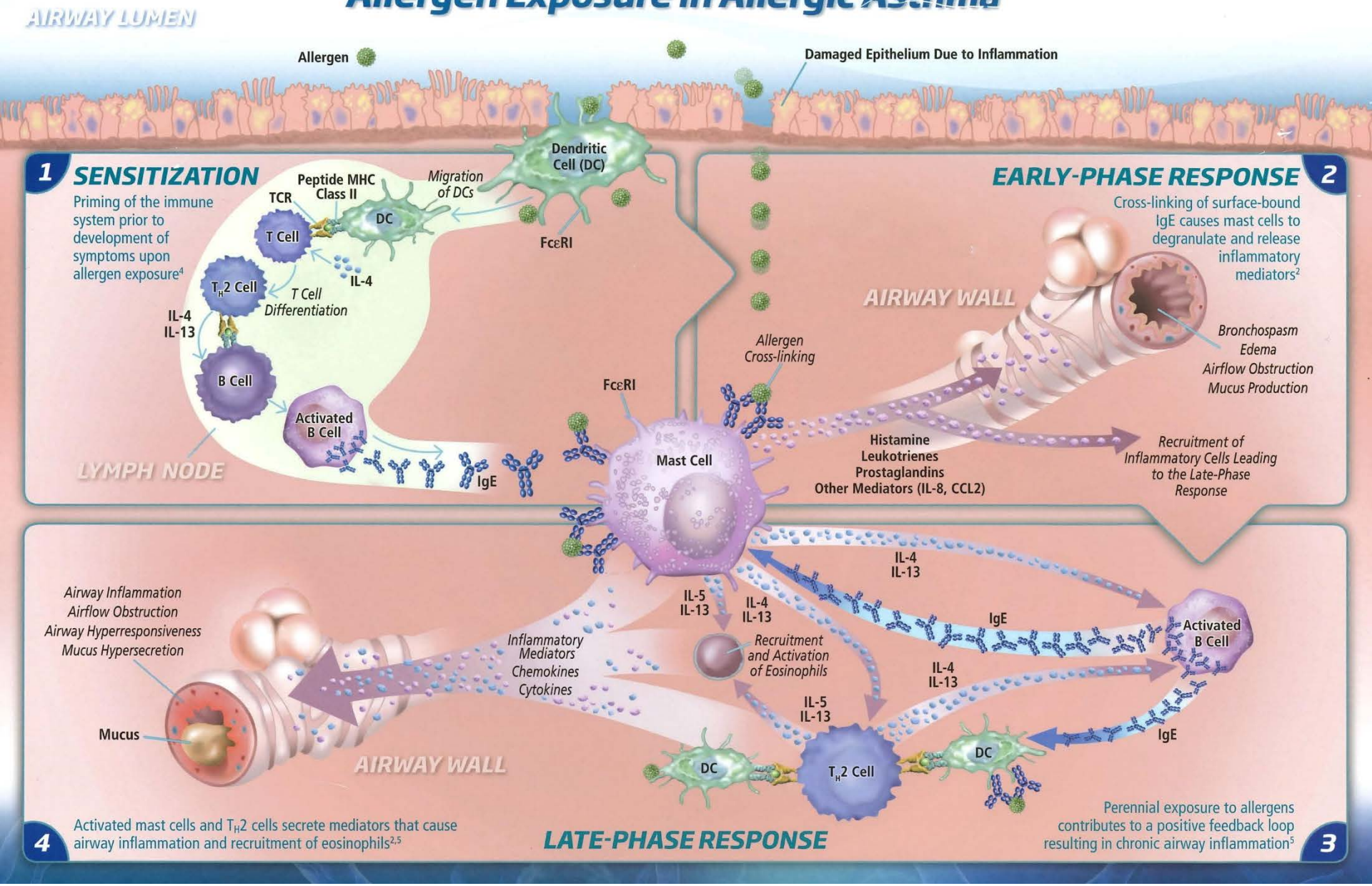


Exposure to Dust Mites and Asthma

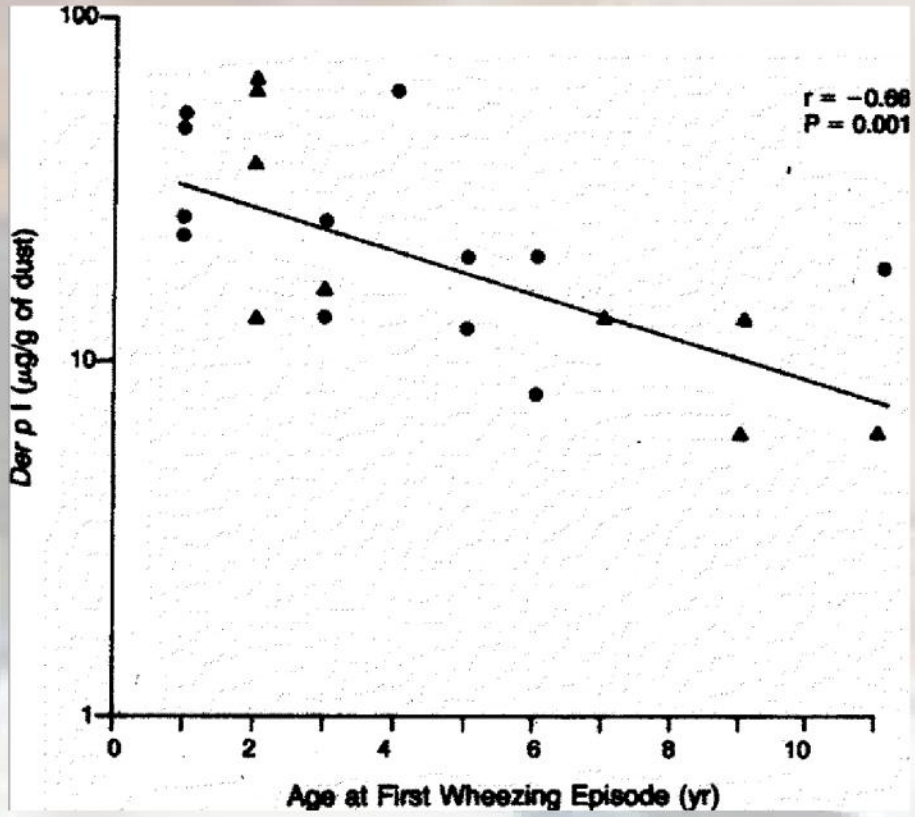
- Children exposed to high level of dust mite antigen at age 1 year were likely to have developed atopic asthma by age 11 yr

  Sporik R *et al NEJM* 1990; 323: 502-7

- Environmental controls for dust mite exposure often incomplete considering presence of dust mite antigen in carpeting and parent's bedding

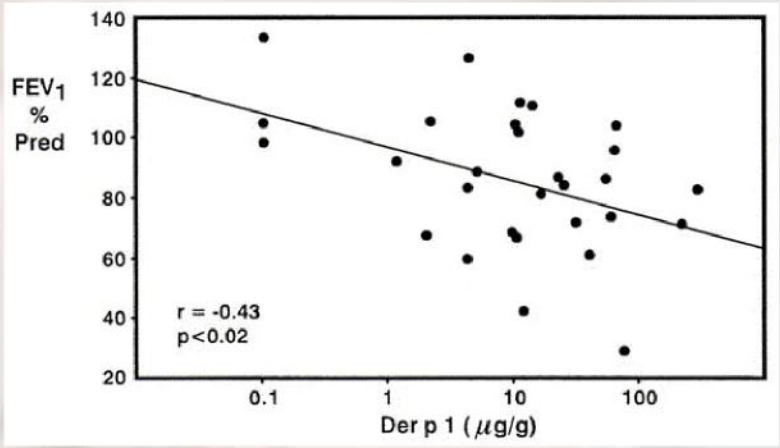
Dust Mites and Asthma

Asthma development in children



Sporik *et al*. NEJM 1990;323:502-7.

Lung function in adult asthmatics



Custovic et al, JACI 1996;98:64-72

Bed Covers for Adults with Asthma

Methods: **Randomized double blind placebo controlled study of allergen impermeable mattress covers.**

Results:

- **Mite allergen lower for the active than placebo group at 6, but not 12 months.**

Conclusion: **Mattress covers alone are not sufficient to control asthma symptoms in allergic adults.**

Woodcock *et al.* NEJM 2003;349:225-36.

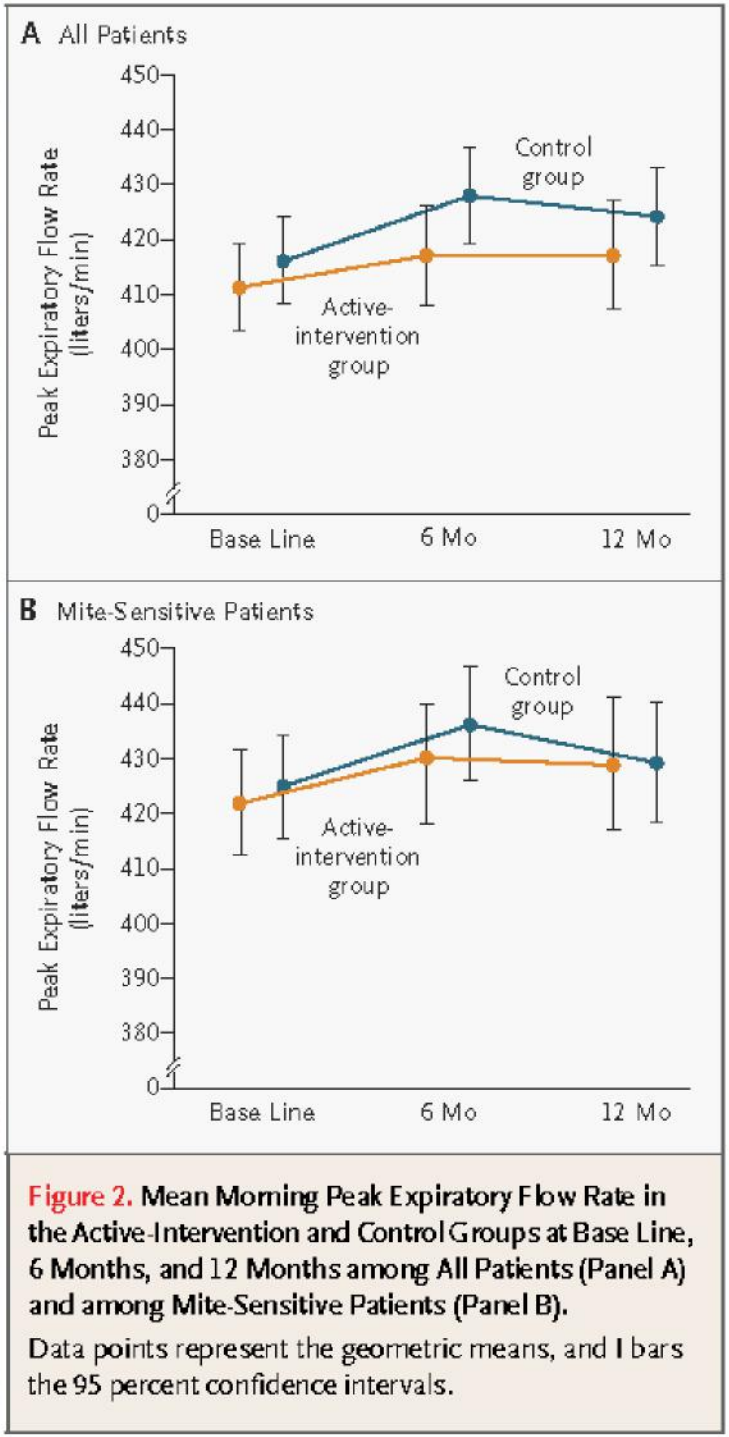


Figure 2. Mean Morning Peak Expiratory Flow Rate in the Active-Intervention and Control Groups at Base Line, 6 Months, and 12 Months among All Patients (Panel A) and among Mite-Sensitive Patients (Panel B).

Data points represent the geometric means, and I bars the 95 percent confidence intervals.

How 'Bout Them Animals?

- **Study of the development of asthma and atopy in children raised with cats and/or dogs**
  - **Boys raised with animals present since birth were less likely to develop allergies (as measured by prick skin testing) to those animals compared to girls**
  - **Methacholine sensitivity improved in boys but not girls**
    - **However, girls were less likely to develop sensitivities to indoor aeroallergens and atopy overall if raised with animals**
  - **Significance only achieved if 2 or more animals in house**

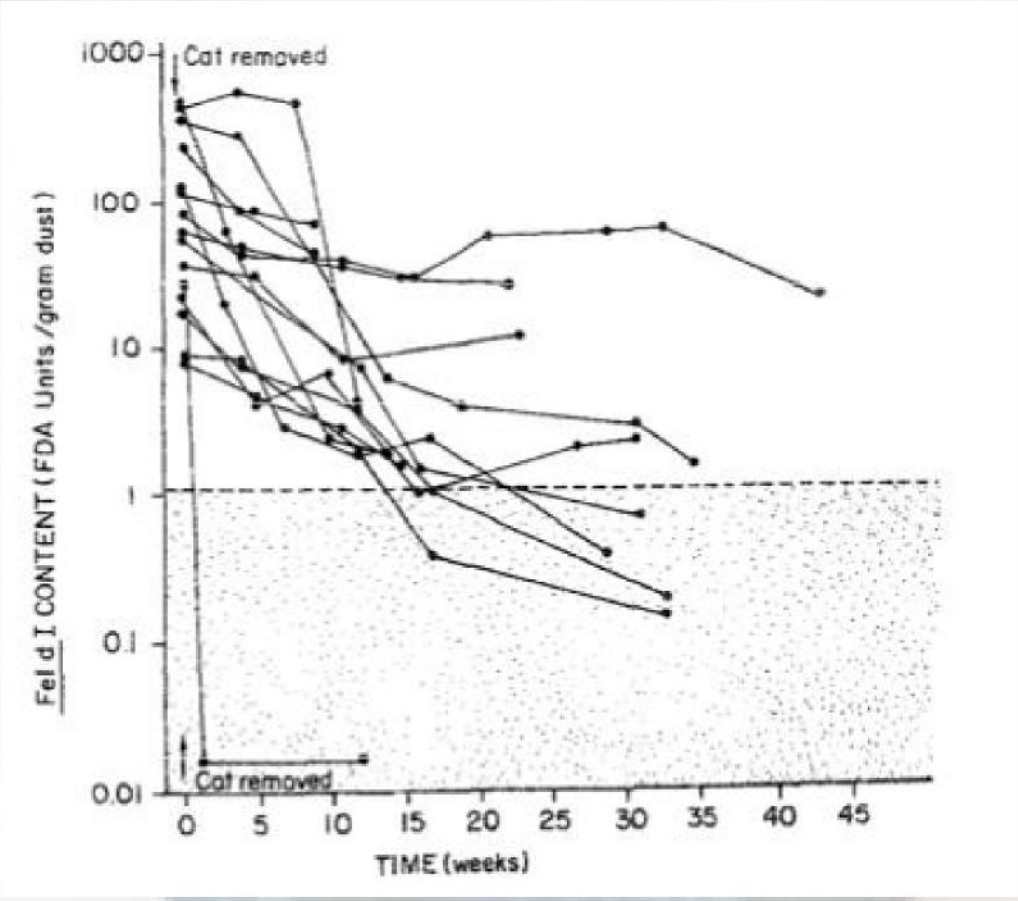
Ownby D et al JAMA 2002; 288: 963-72

Cat Allergen and Asthma Morbidity in Adult Women Who Own Indoor Cats

	Steroid Use		ER Visit		Wheeze, No Cold	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Low exp. or not sens.	1.0	1.0	1.0	1.0	1.0	1.0
High exp. and sens.	2.8 (1.2-6.4)	2.7 (1.2-6.2)	1.6 (0.3-8.4)	1.7 (0.3-9.8)	5.6 (2.7-11.6)	6.8 (3.3-14.0)

Lewis et al. AJRCCM 2002;165: 961-66.

Cat Allergen in Home Declines Slowly After Pet Removal

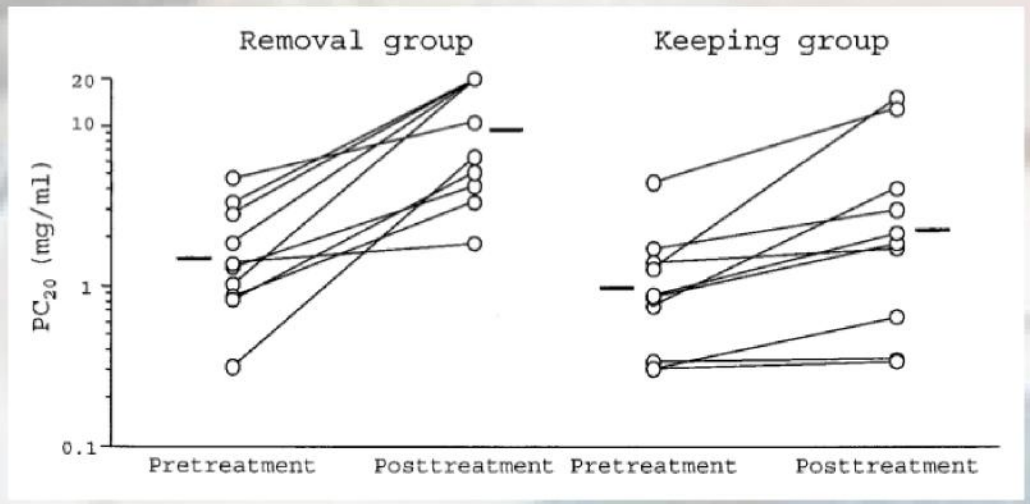


Fel d 1 content in the dust from homes after removal of a cat

Wood et al JACI 83:730,1989

Effect of Pet Removal on Asthma Morbidity

- **Prospective observational study of 20 asthmatic pet allergic adults**
- **10 elected to remove pets, 10 kept pets**
- **Followed for** ≥ 1 year
- **5/10 - * 0/10 on ICS in removal group**
- **6/10 - * 9/10 on ICS in keeping group**



Shirai et al Chest 2005;127:1565-71.

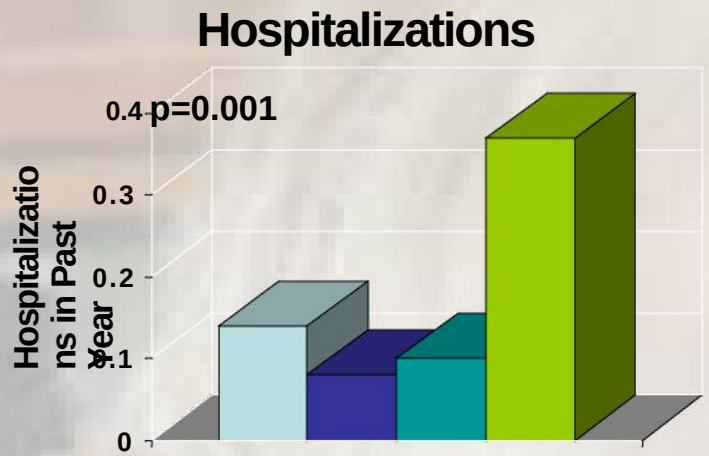
Cockroach Allergen Exposure

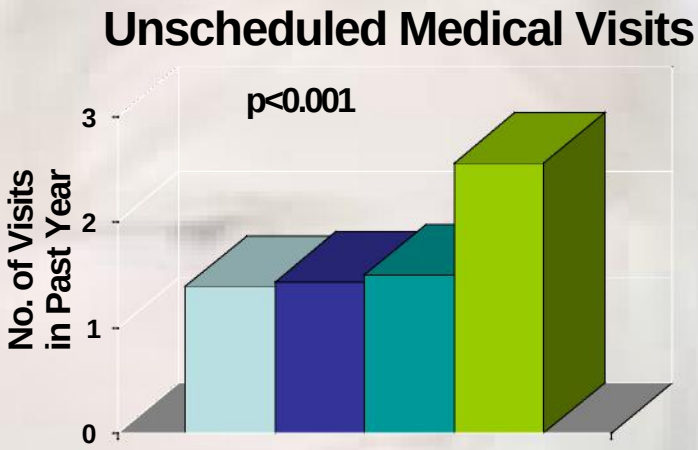
Risk Factors for High Bla g 1 Levels

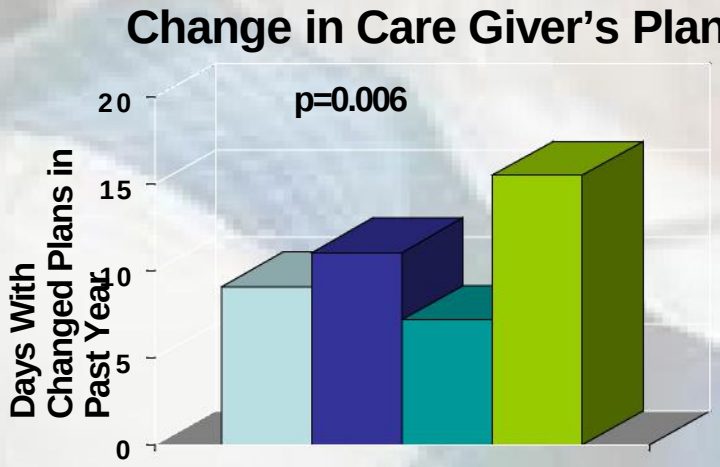
Risk Factor	Odds Ratio (95% CI)
Type of dwelling	
Detached	Reference
High rise apartment	70.0 (16.6-295.9)
No of units in building Single family Multifamily	Reference 4.89 (1.87-12.8)
Construction year	
1978-1998	Reference
pre-1940	3.29 (0.87-12.4)
Urbanization	
population < 1 million	Reference
population > 1 million	3.15 (1.06-9.37)
Household income	
> $60,000	Reference
< $20,000	12.1 (2.05-71.7)

Cohn et al., Environmental Health Perspectives, 114: 522-526, 2006

Cockroach Allergen Exposure and Asthma Morbidity in Inner City Children







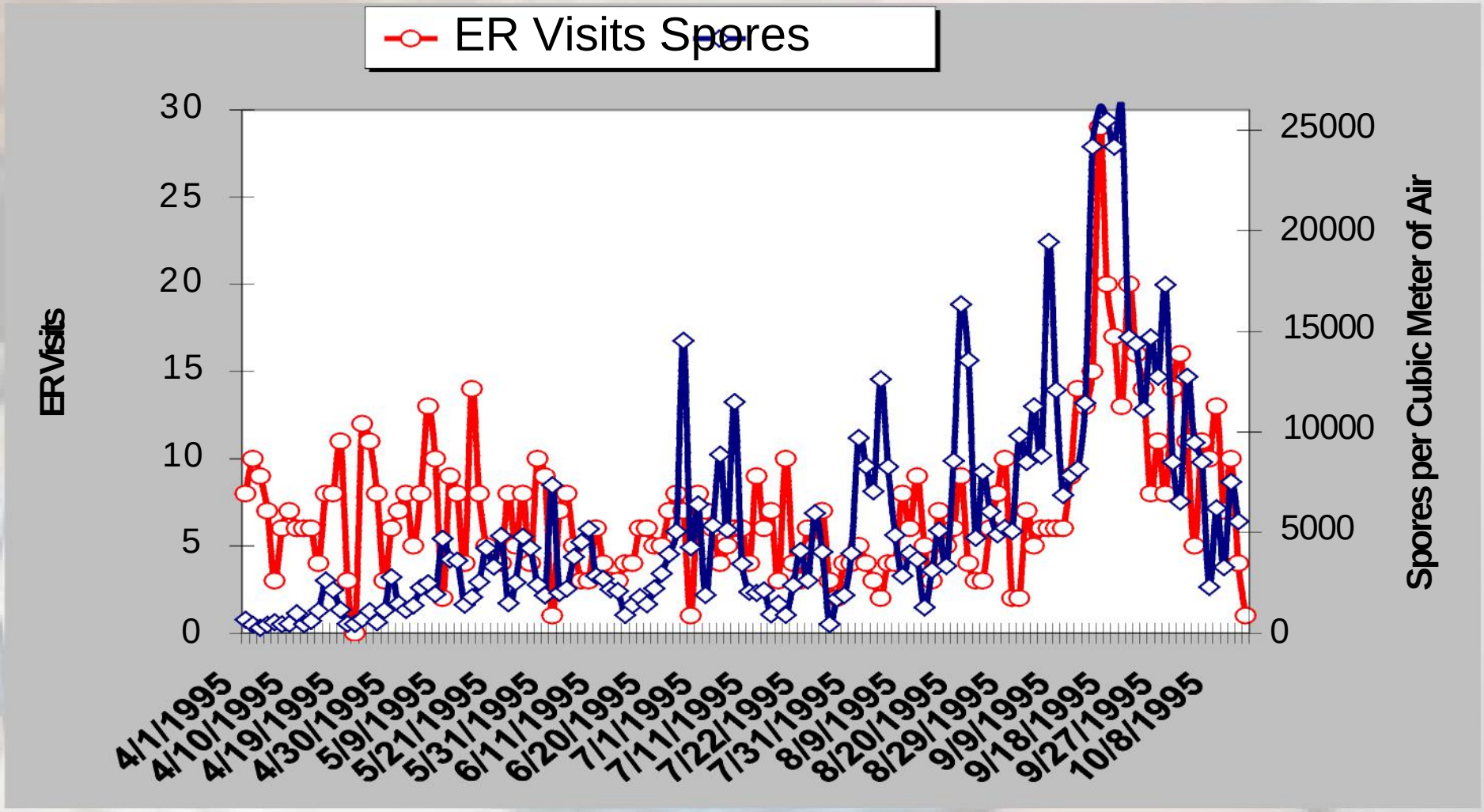
- neg skin test, low allergen exposure
- neg skin test, high allergen exposure*
- pos skin test, low allergen exposure
- pos skin test, high allergen exposure*

* Blag 1 > 8 U/gram

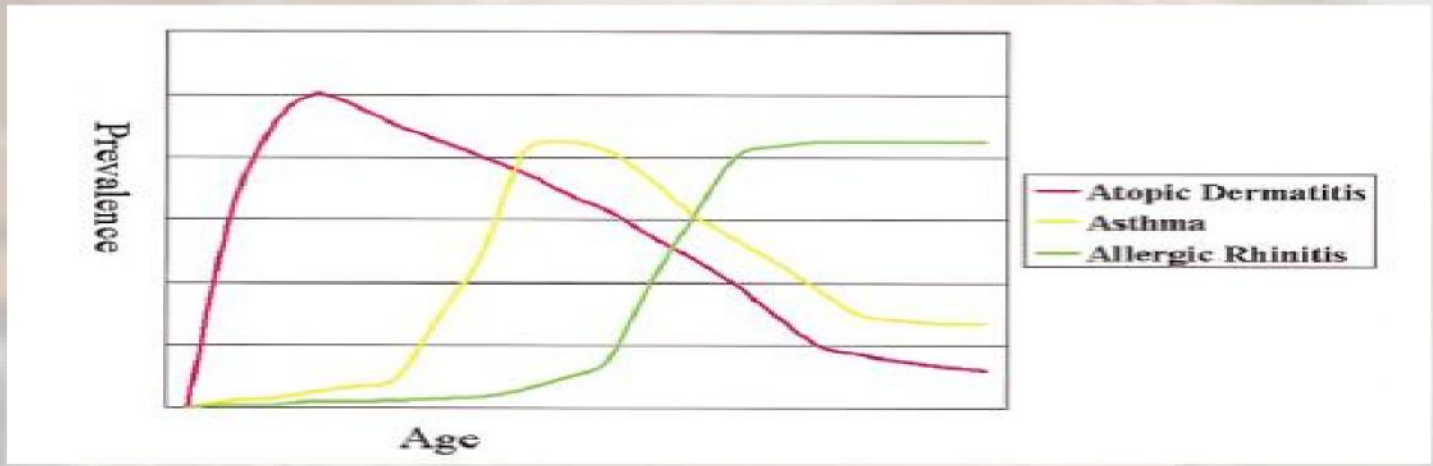
Rosenstreich et al., N Eng J Med, 336: 1356-1363, 1997

Association Between Spore Peaks and Asthma Hospitalizations in Kansas City

- First documented by Salvaggio 1971



The Atopic March



- **Prevalence of AD peaks at 20% at age 1 and declines to 5% by age 22**
- **Prevalence of wheezing increased from 5% at age 1 to 40% by age 22 years**
- **Early sensitization to foods in 1st year of life (odds ratio 12.3) or aeroallergens (OR 4.6) by year 2 increased risk of asthma by adulthood**

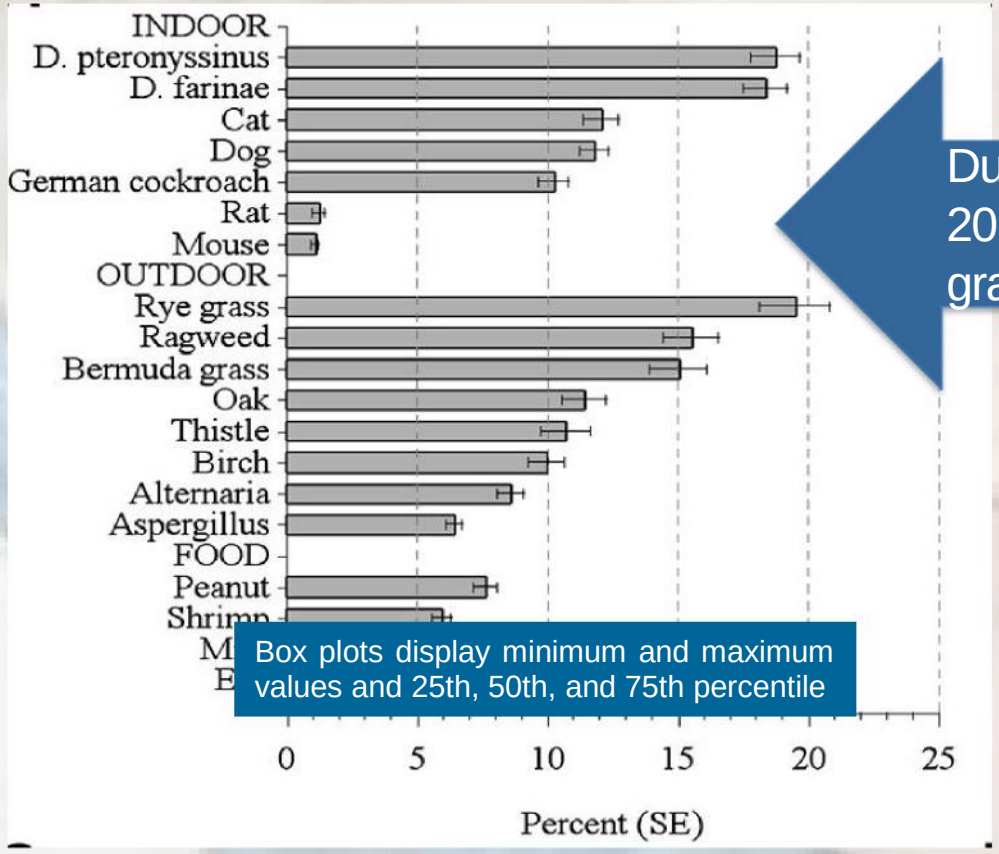
Rhodes HL *et al J Allergy Clin Immunol* **2001; 108: 720-5**

Allergy Testing

Prevalence of allergic sensitization per Allergy Blood Tests Serum Specific- IgE (sIgE) Test Results in US Population NHANES IV 2005-2006

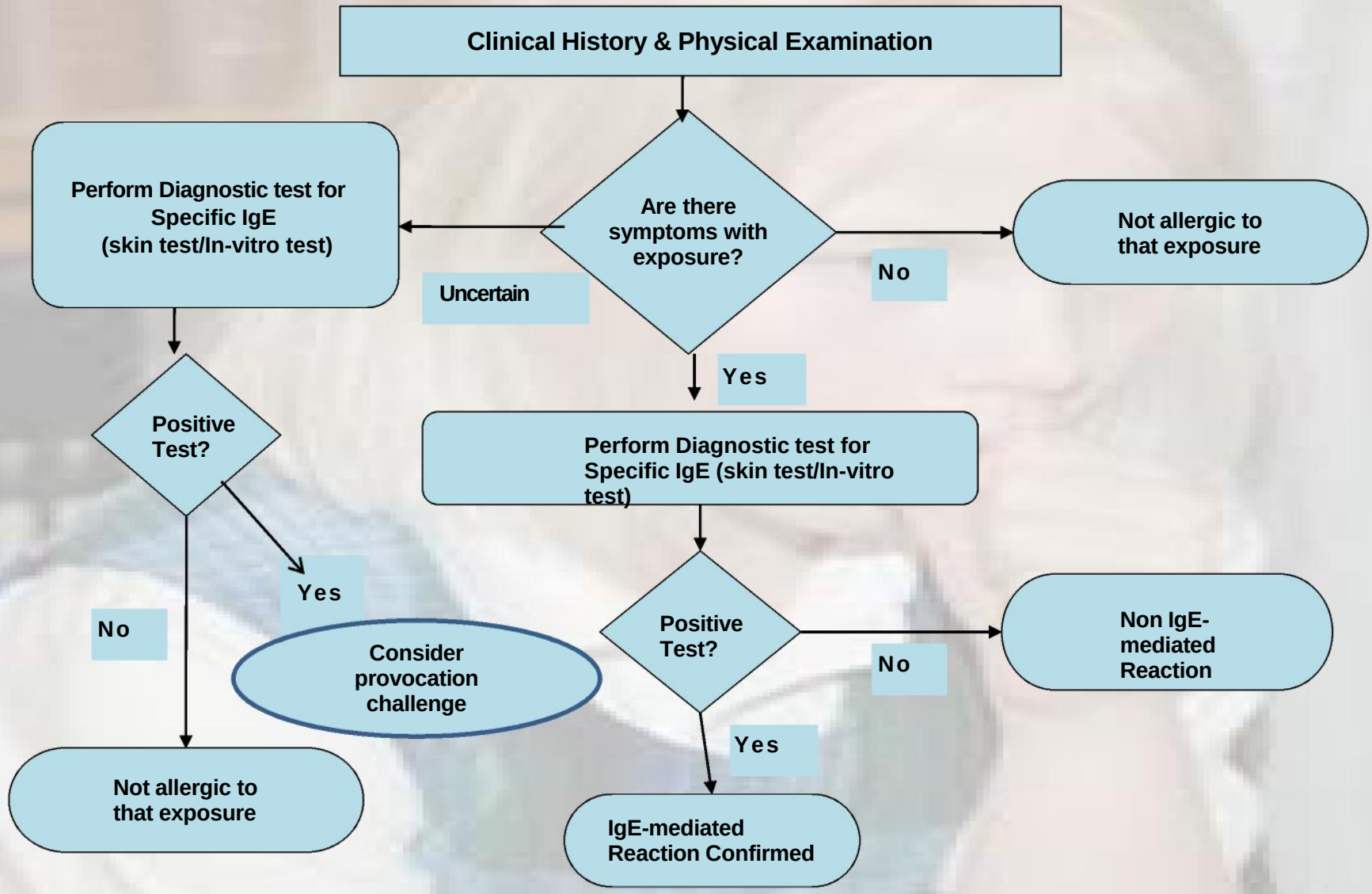
Participants ≥1 year (n = 9440) were tested for serum specific-IgE to a panel of inhalant and food allergens.

- **Prevalence of allergen sensitivities to 19 allergens in the participants ≥ 6 years (N=7268)**



Salo et al, J Allergy Clin Immunol 2014; 134:350-9.

Diagnostic Algorithm for the Assessment of Human Allergic Disease



What Goals Do You Want to Accomplish by Performing Allergy Testing?

- **Desiring "an idea" as to whether or not a baby or young child is atopic**
  - **ImmunoCAP based on age**
    - **Foods for infants with AD – most likely egg, milk, wheat, soy, peanut, tree nut, fish**
    - **Children < 3 years – with AD -> above foods plus dust mites, animal danders, mold screen**
    - **Children < 3 years w/o AD – mites, dander, mold**
    - **Children > 3 years – perennial and major seasonal aeroallergens (cedar, elm, oak, bermuda, timothy, ragweed, pigweed)**

What Goals Do You Want to Accomplish by Performing Allergy Testing?

- More definitive identification of allergens in children > 2years
  - Skin testing by ABAI certified allergist
  - If PCP ask yourself how comfortable you will be in explaining the results to patient or parent
    - Testing tools available from manufacturers – MultiTEST, GreerPiks, Duo-Tip, Comforten, etc
    - Recognition of false positives in dermatographic patients
    - Reasons for falsely negative testing (meds, age)

How Does Immunotherapy Work?

Does it Matter Where the Antigen is Administered?

Subcutaneous

- Administered in one or more injections quickly
– “Depot” allows for tissue dendritic cells to access and uptake
– Other inflammatory cells infiltrate (late phase response) – Optimal dosages defined for standardized allergens
– Rare fatalities reported

Sublingual

–Must be held under tongue for 1 to 2 minutes to be effective
–Langerhanscells uptake by pinocytosissmaller peptide fragments
–Larger dosages required
–Dilutionaleffect of multi-allergens may effect response
–No benefit for hymenoptera
–No fatal reactions reported (yet) –a few category IV’s

Bottom Line SCIT

Effective when ideal (high dose) maintenance concentrations achieved

–At maintenance, monthly dosing intervals make SCIT cost effective

–Effective dosage achieved per dose and not cumulative dosing

–Promotes development of T regulatory cells that produce IL-10 and TGF-beta responsible for shifting naïve T cells away from T2 pathway

–Rare risk of anaphylaxis

Effectiveness of SLIT

- **Extensive reviews of most studies document**
  - **Best benefits (e.g., symptom scores, medication usage) start in second year / season of use despite pre-seasonal rush / rapid updosing**
  - **Initial rise in allergen-specifc IgE seen in the first year followed by gradual decline in subsequent years of use**
  - **Studies are small with high (upwards of 25%) drop-out rates in both active and placebo arms**

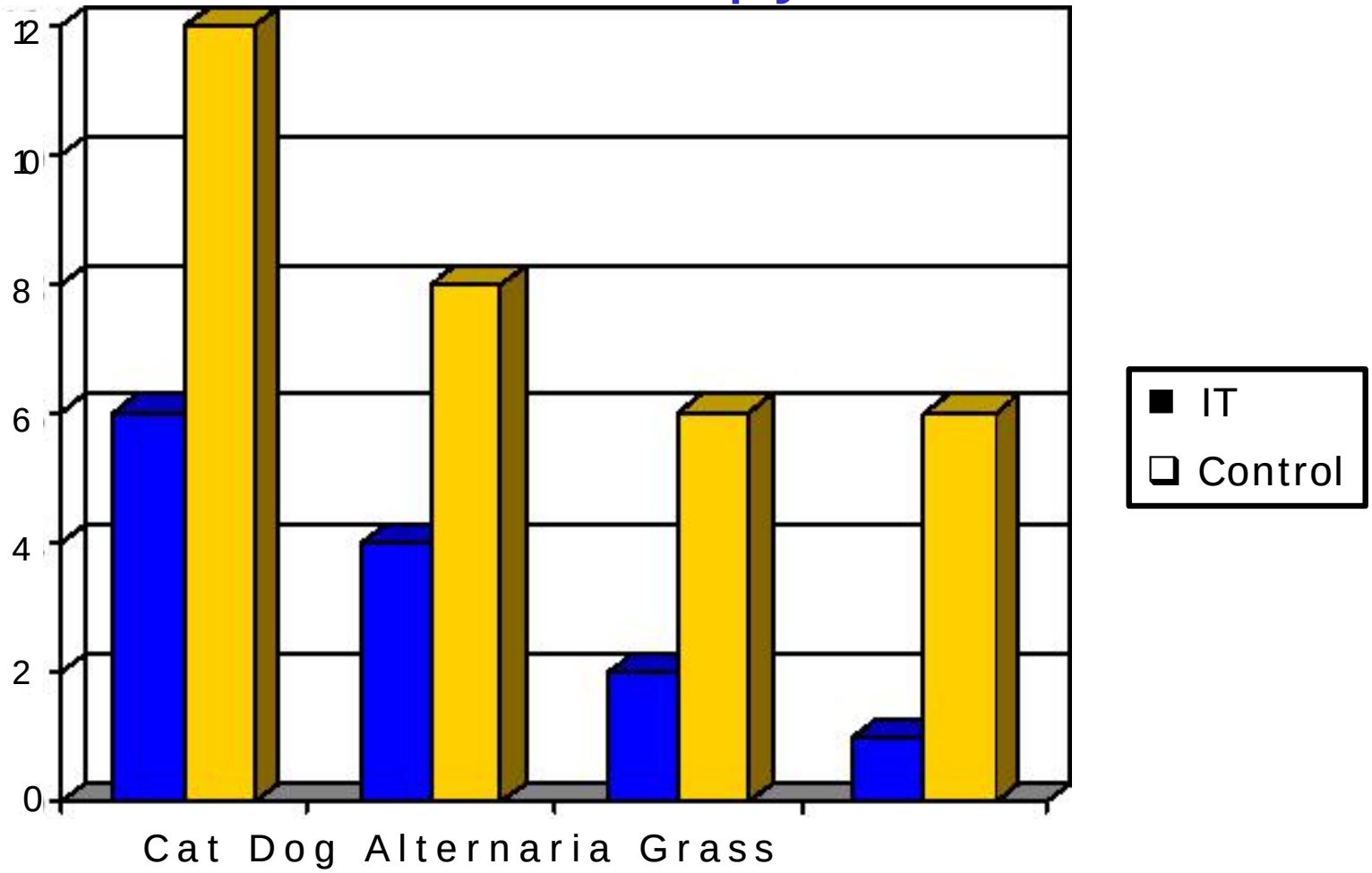
Bottom Line SLIT

- **Effective alternative to SCIT**
- **Safer than SCIT – no fatalities reported**
  - **– Bronchospasm reported frequently – caution with subsequent dosing**
- **As with SCIT, effective dosing only at high dosages and dosages taken daily to QOD**
  - **– Unlike SCIT, dosing intervals cannot be increased**
  - **– Unlike SCIT, multi-antigen in one vial may reduce effectiveness**
  - **– Unlike SCIT, SLIT drops not FDA approved**

Why Immunotherapy?

Only Therapy Available to Change Immune Response Longterm

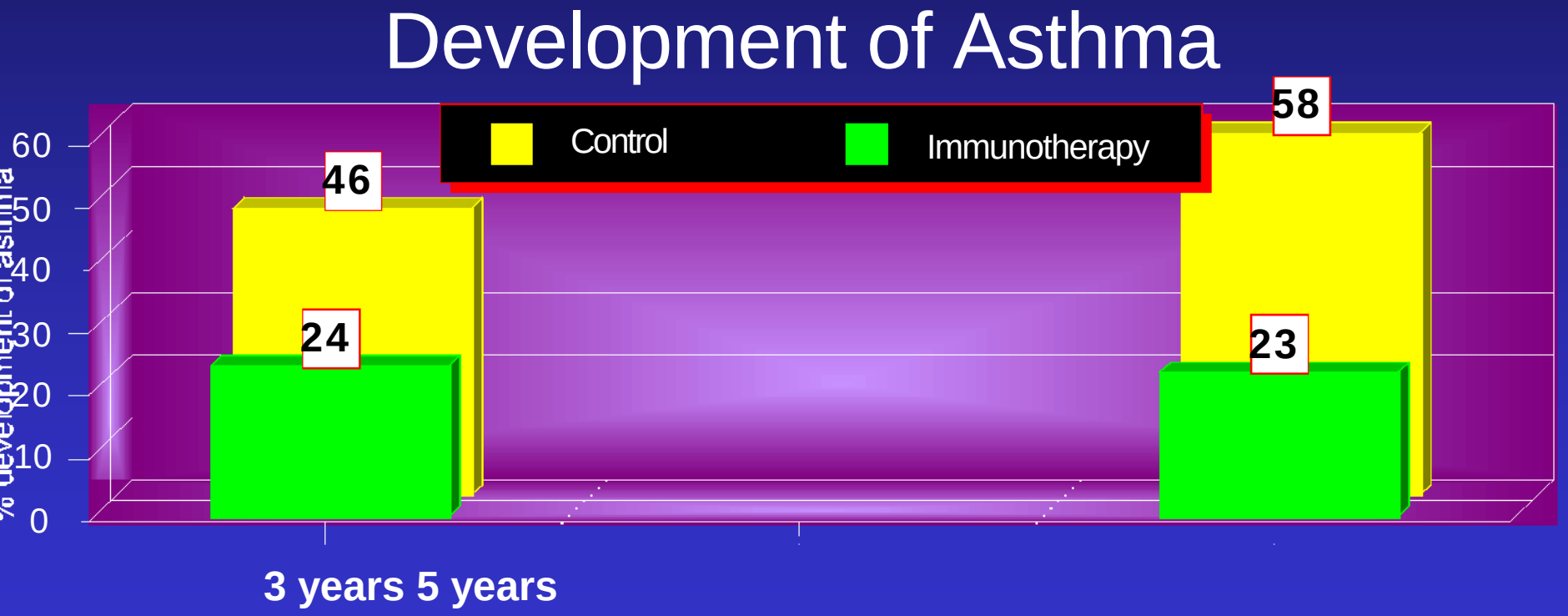
Prevention of new sensitivities after HDM immunotherapy in children



Des Roches A. *et* at. JACI 1997;99:450-53

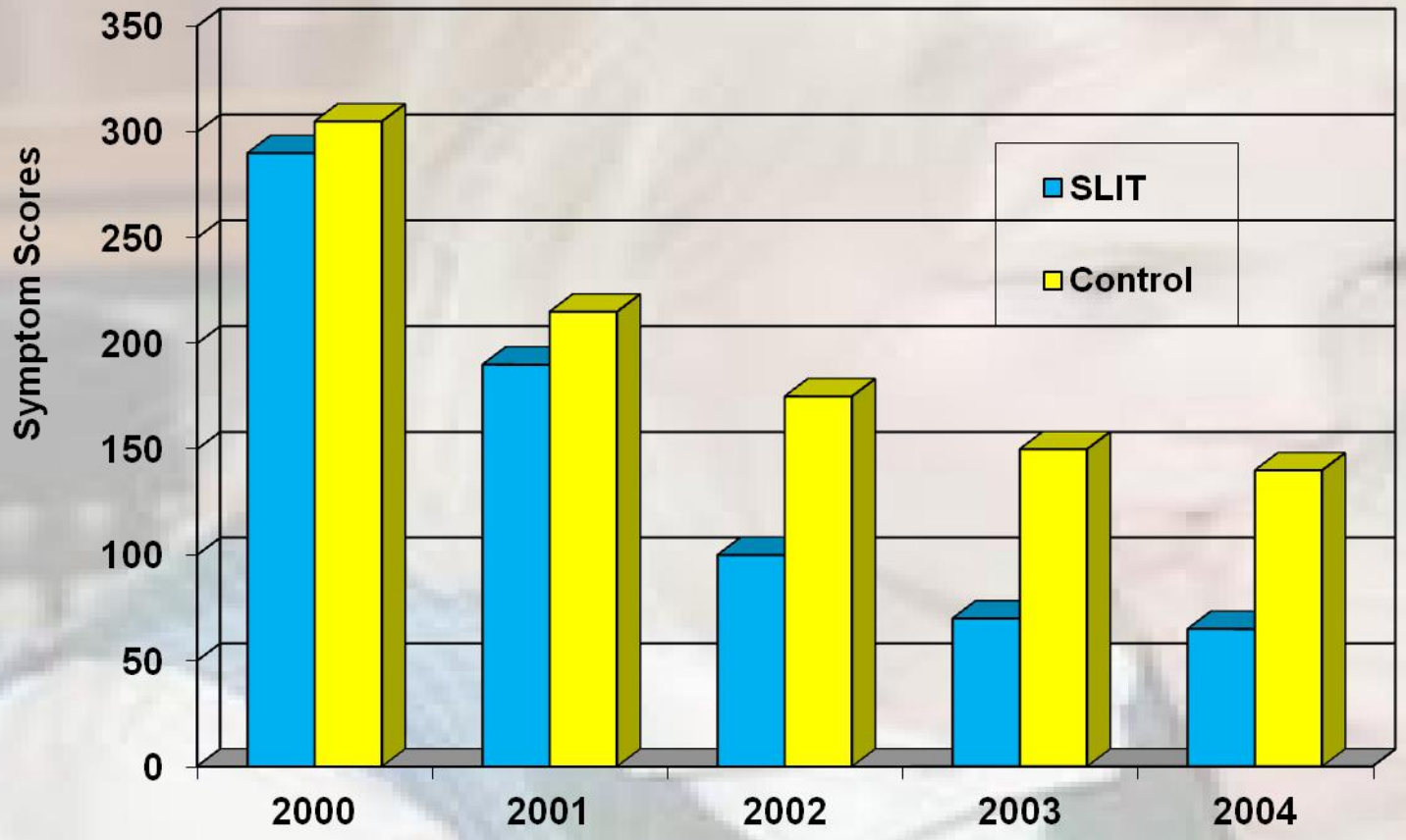
Prevention of Asthma by Immunotherapy

ospective study with 205 children, 6 and 14 years mean age 10.7),with AR to birch and/or grass to etermine if specific immunotherapy can prevent the evelopment of asthma



oller, C et al. J Allergy Clin Immunol 2002; 109: 189-294.

Birch Pollen Induced Asthma



102 mcg per year of birch extract for 3.5 years

Significant declines in symptom scores ($p<0.001$) compared to baseline year (2000)

Marogna M *et al JACI* 2005; 115: 1184-1188

Stepwise management, SLIT as an add-on option for some patients

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV_1 is 70% predicted
- Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT: sublingual immunotherapy

Other Therapeutic Options

For Both Allergic and Non-Allergic Asthma Phenotypes

Table 1. Biologic Agents in Asthma and Potential Biomarkers

Pathway	Biologic Agents Approved or in Trials	Biomarkers Predicting Response to Therapy	Biomarkers Modulated by Therapy	Reference(s)
IgE	Omalizumab	F_{ENO} Blood eosinophils Periostin	F_{ENO} Sputum eosinophils	Hanania *et al.*, 2013 (63)
IL-4/IL-13	Pitrakinra (competitive antagonist) Dupilumab (receptor antibody)	F_{ENO} Sputum eosinophils Blood eosinophils	F_{ENO}	Wenzel *et al.*, 2007 (81) Wenzel *et al.*, 2013 (60)
IL-13	Lebrikizumab Tralokinomab	Periostin F_{ENO} Eosinophils Sputum IL-13 (periostin surrogate)	F_{ENO}	Corren *et al.*, 2011 (61) Piper *et al.*, 2013 (62)
IL-5	Mepolizumab Reslizumab Benralizumab	Sputum eosinophils Blood eosinophils	Sputum eosinophils Blood eosinophils	Flood-Page *et al.*, 2007 (25) Haldar *et al.*, 2009 (57) Pavord *et al.*, 2012 (58) Bel *et al.*, 2014 (59) Nair *et al.*, 2009 (66) Ortega *et al.*, 2014 (74) Castro *et al.*, 2011 (75) Castro *et al.*, 2014 (76)

Definition of abbreviation: F_{ENO} = fractional exhaled nitric oxide.

Bottom Line

- **One size does not fit all – PHENOTYPES**
- **Asthma is dynamic and complex**
- **The immune response (allergic or not) changes the playing field such that we are in a constant guessing mode**
  - **– Allergy to cat dander may not respond solely to home environmental controls due to dander elsewhere**
  - **– Viral infections provoke a different immune response that may complicate the original picture**

Bottom Line

- **Identification of children at risk of asthma allows for earlier intervention**
  - **Children with atopic dermatitis**
  - **Children with asthmatic parent**
- **Accurate allergy testing for defining control measures and potential immunotherapy**
  - **SCIT currently approved by FDA**
  - **SLIT more convenient if done correctly**