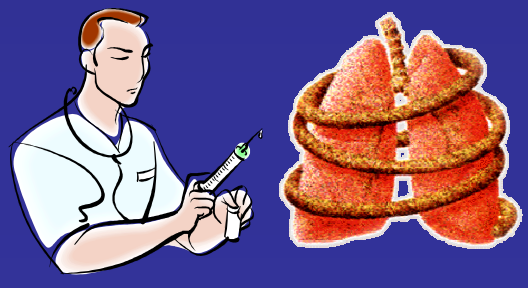
Ο ρόλος της ανοσοθεραπείας στην αντιμετώπιση του άσθματος. Πότε και με τι όφελος;

Αικατερίνη Συρίγου M.D.

Αλλεργιολόγος

Συντονίστρια Διευθύντρια Αλλεργιολογικού Τμήματος

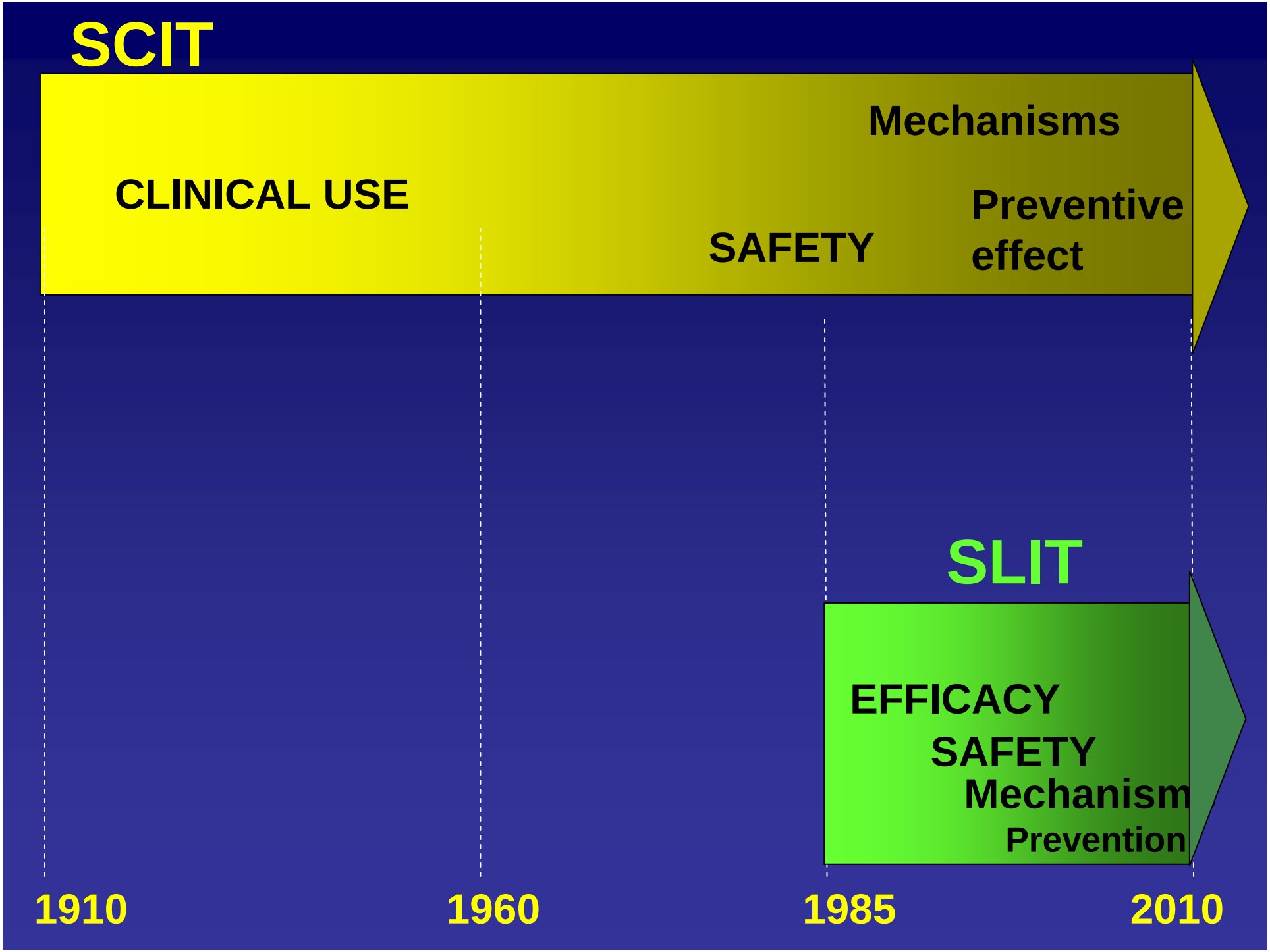
Γενικό Νοσοκομείο Νοσημάτων Θώρακος Αθηνών «Η Σωτηρία»

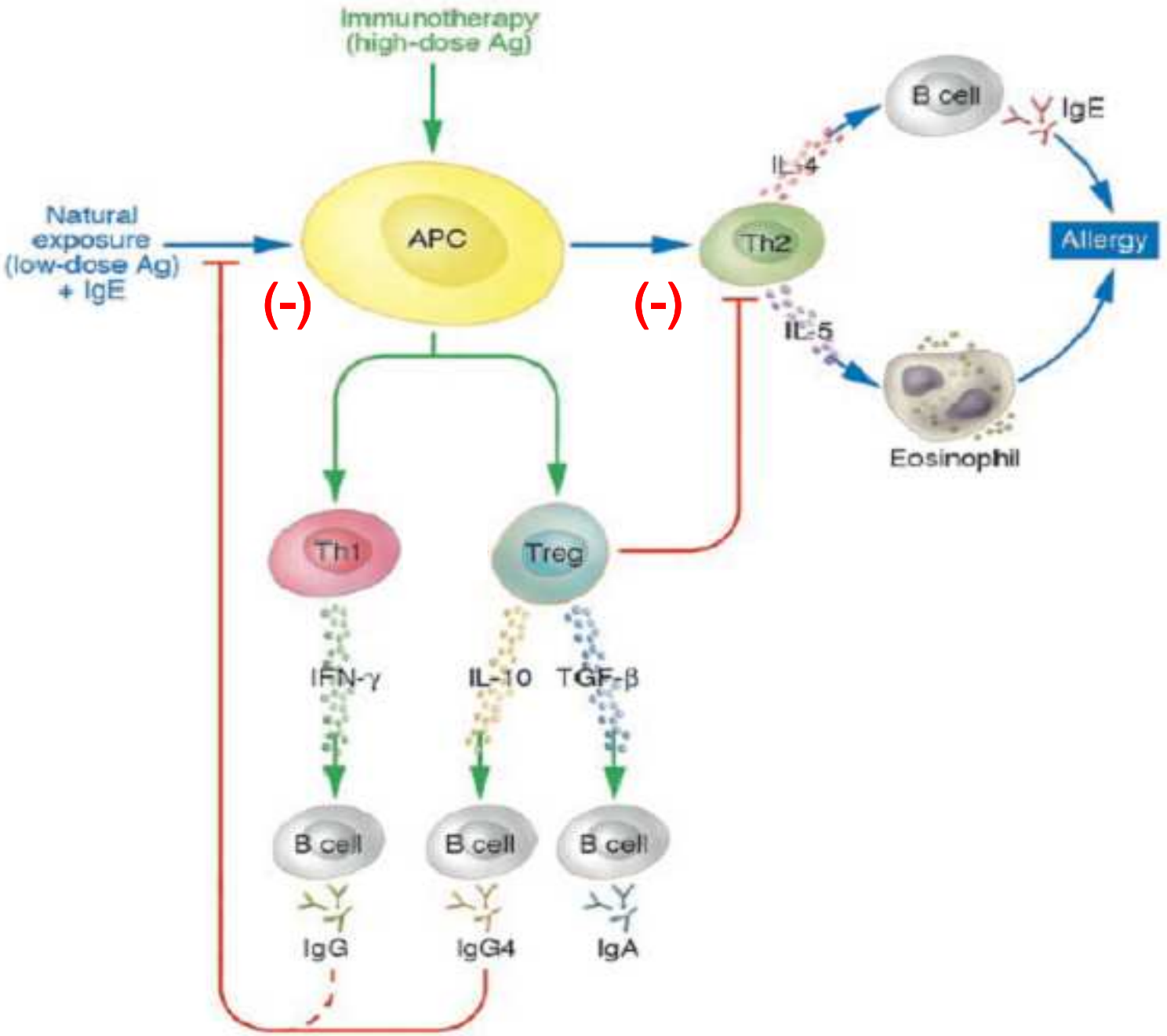


Ειδική Ανοσοθεραπεία

- Είναι η επαναλαμβανόμενη χορήγηση ειδικών αλλεργιογονικών εκχυλισμάτων, σε ασθενείς με επιβεβαιωμένη IgE μεσολαβούμενη αντίδραση, με σκοπό την ελάττωση ή αναστολή των IgE μεσολαβούμενων ανοσολογικών αντιδράσεων.

Cox L, et al. JACI 2011


SCIT
Mechanisms
CLINICAL USE
Preventive
effect
SAFETY
SLIT
EFFICACY
SAFETY
Mechanism
Prevention
1910
1960
1985
2010



Robinson DS, et al; Tregs and allergic disease. J Clin Invest 2004; 114: 1389.

Αποτελέσματα ανοσοθεραπείας

✓ **Αντισωματική απάντηση:**

- ⬆ IgG1, IgA
- ⬆ Blocking IgG4 (*Ανταγωνισμός IgE*)

✓ **Τ-κυτταρική απάντηση:**

- **PBMCs:**
  - ⬇ IL-4 mRNA
  - ⬆ IL-10
- **Στους ιστούς:**
  - ⬆ IL-12 mRNA, ⬆ IFNγ mRNA
  - ⬇ IL-4 mRNA, IL-5 mRNA

✓ **Απόπτωση Th2-κυττάρων (activation-induced cell death)**

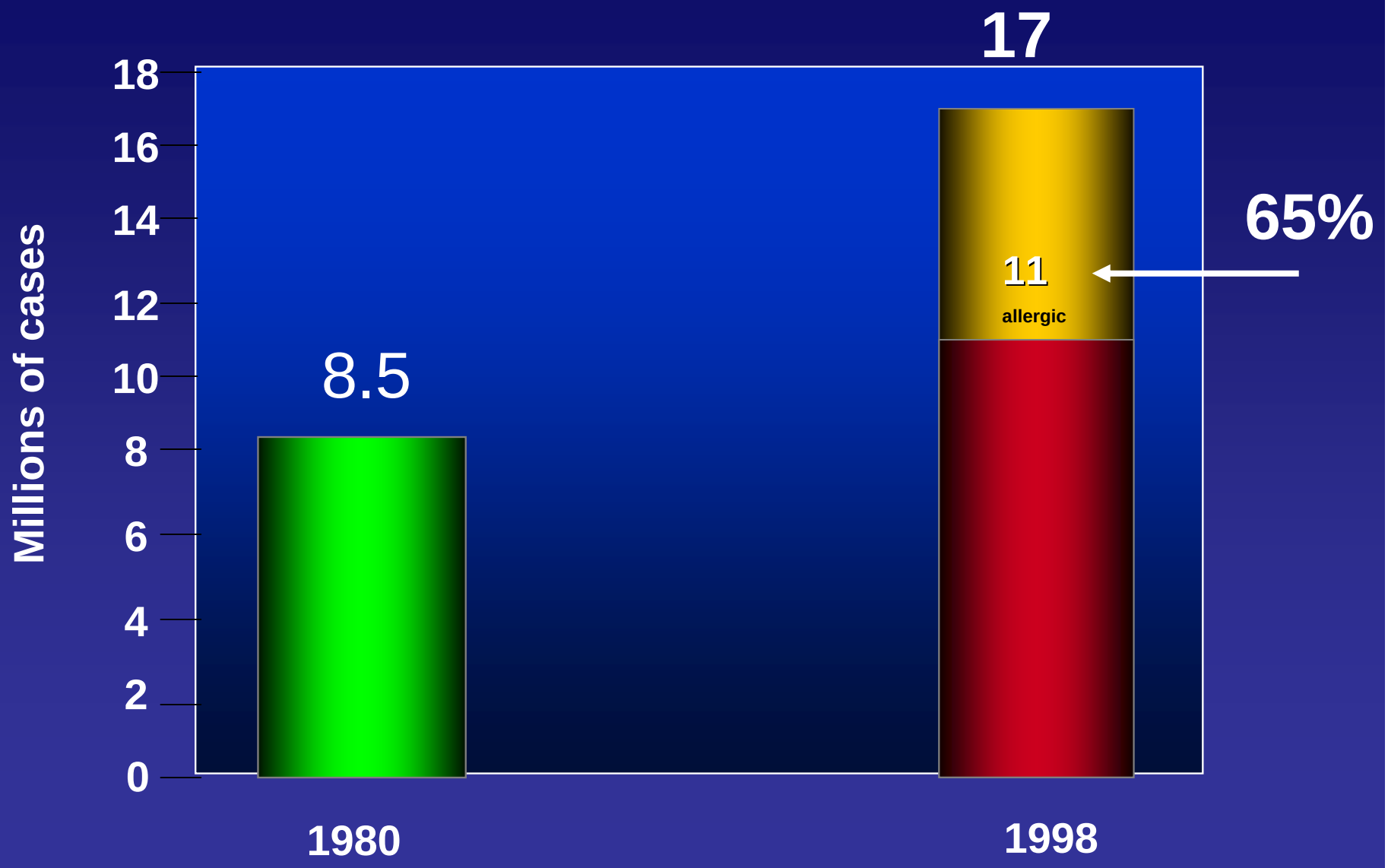
Akdis M, et al. JACI, 2007; 119: 780

Ενδείξεις της ανοσοθεραπείας

- Ενδείκνυται για το χειρισμό ασθενών με IgE μεσολαβούμενα νοσημάτα:
  - Αλλεργία στο δηλητήριο υμενοπτέρων
  - Αλλεργική ρινοεπιπεφυκίτιδα
  - **Αλλεργικό άσθμα**
- Αντενδείκνυται:
  - ΚΝ/ΑΟ
  - Νοσήματα χωρίς IgE μηχανισμό

Cox L, et al. JACI 2011

The Asthma Epidemic



CDC-NIH Morbidity and Mortality Weekly Report

Incidence of Allergic Asthma

Asthma related to allergies:
90% in children
50-65% in adults

Συσχέτιση μεταξύ αλλεργικής ρινίτιδας και άσθματος

- Αλλεργική ρινίτιδα διαγιγνώσκεται στο 80% των ασθενών με άσθμα
- Άσθμα διαγιγνώσκεται στο 30% των ασθενών με αλλεργική ρινίτιδα

G. Passalacqua Clin. Exper.Allergy, 2011 (41) 1247–1255.
A. Cruz et al.Allergy 2007: 62 (Suppl. 84): 1–41.

Prevalence of rhinitis among asthmatics

Authors	Location	Number of individuals studied	Study design	Proportion of rhinitis in asthmatics	Comments
Leynert et al. (6)	France	850 adults	Cross-sectional	78%	Quality of life impaired in rhinitis
Shamssain and Shamsian (8)	England	3000 children	Cross-sectional	53% in boys 63% in girls	Nothing remarkable
Montnemery et al. (9)	Sweden	12 079 adults	Cross-sectional by postal questionnaire	46%	'Significant nasal symptoms'
Celedon et al. (10)	China	10 009	Cross-sectional	6.2%	Within a cohort
Terreehorst et al. (15)	The Netherlands	164	Cross-sectional	92%	Nothing remarkable
Linneberg et al. (11)	Denmark	743	Longitudinal	100%	Two evaluations 8 years apart
Sichletidis et al. (13)	Greece	2005 children	Cross-sectional	69%	33% of rhinitics had asthma
Leynaert et al. (113)	Europe	90 478	Cross-sectional	74–81%	Nothing remarkable

A. Cruz et al.Allergy 2007: 62 (Suppl. 84): 1–41

Clinical effects in terms of step-down rate after rush IT in house dust mite-sensitive asthmatics

	FEV_1%		Duration	
	≥70%	<70%	≥10 y	<10 y
Unchanged:	15 (39.5%)	8 (66.7%)	18 (54.5%)	5 (29.4%)
Improved:	23 (60.5%)	4 (33.3%)	15 (45.5%)	12 (70.6%)
	$P = 0.009$		$P = 0.043$	

Nagata M, et al Intern Med 1993;32:702-9.

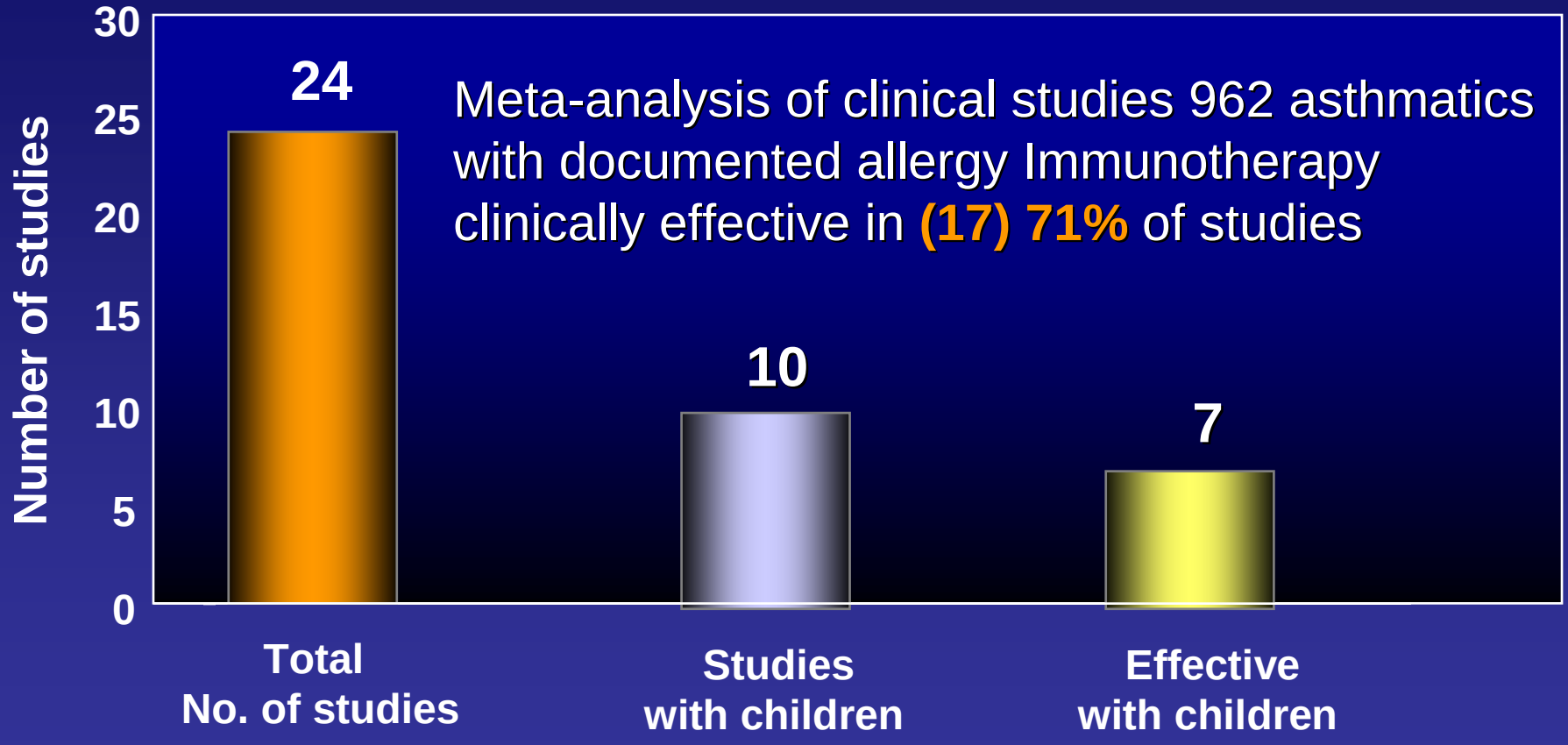
Improvement of symptoms and reduction in medication and BHR after IT in 20 randomized placebo-controlled trials (1954-1990)

Outcome measure	Dust mite OR, (95% CI)	Other allergens OR, (95% CI)	All Allergens OR, (95% CI)
Symptom Improvement	2.7 (1.7 – 4.4)	4.8 (2.3-10.1)	3.2 (2.2-4.9)
Reduction in medication	4.2 (2.2-7.9)	ND	ND
Decreased BHR	13.7 (3.8-50)	5.5 (2.8-10.7)	6.8 (3.8-120)

CI: confidence Interval; ND: not done; OR: odds ratio

Abramson MJ, et al. Am J Respir Crit Care Med 1995; 151: 969-974

What's the Evidence?



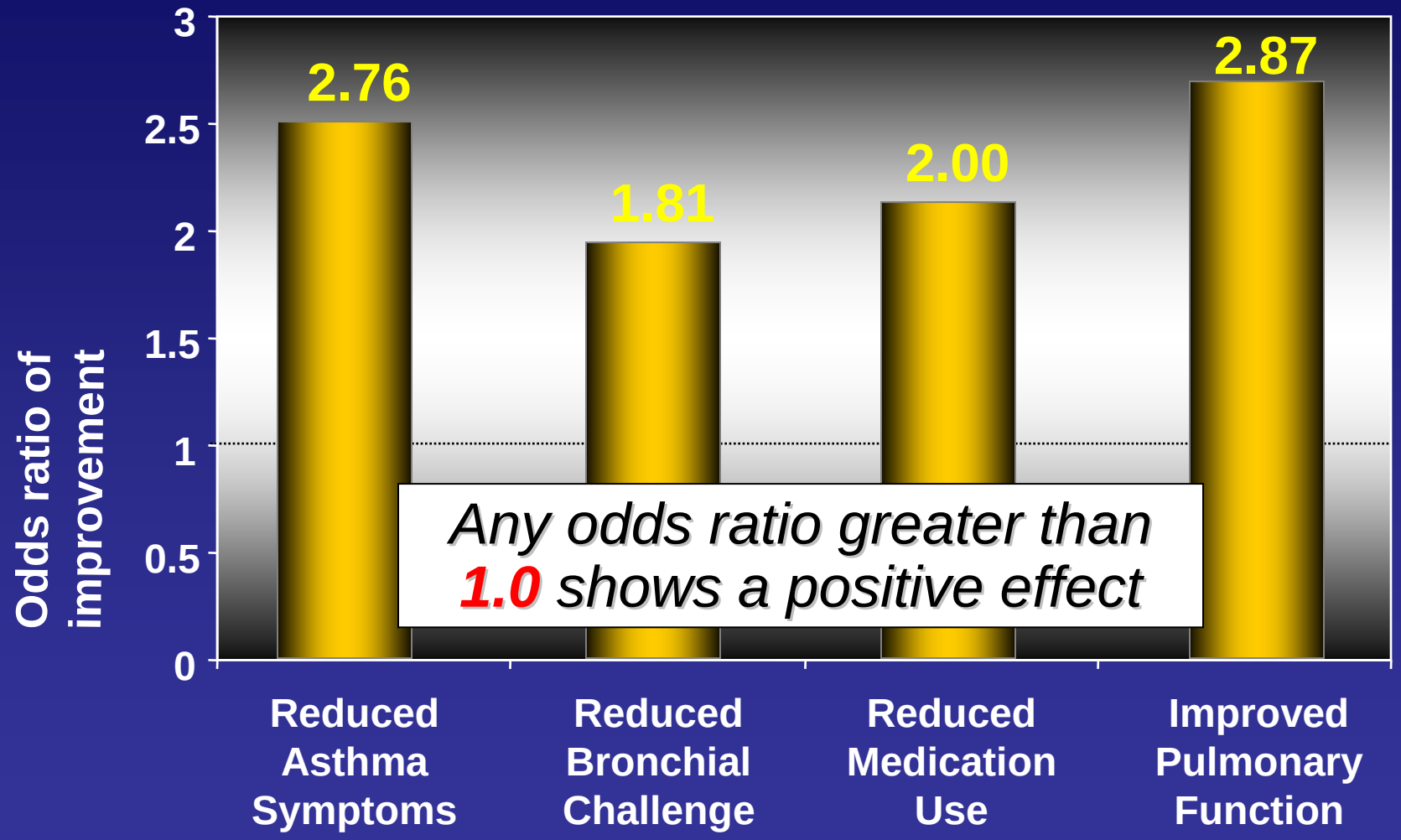
Ross RN, Nelson HS, Finegold I. Clin Ther 2000

Meta-Analysis Results

Study	Effective	Ineffective	Equivocal	Total
Adults only	9	1	2	12
Children only	7	3	0	10
All Ages	1	0	1	2
TOTAL	**17**	**4**	**3**	**24**

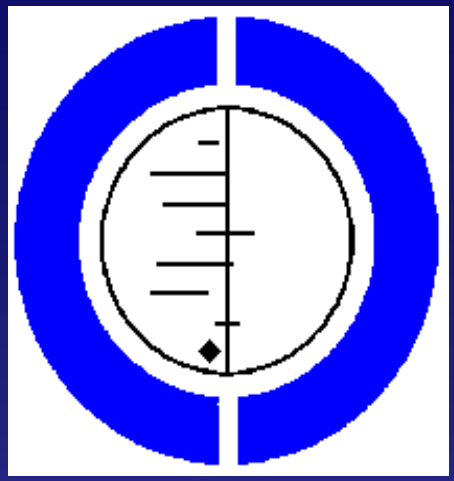
Ross RN, Nelson HS, Finegold I. Clin Ther 2000

Effectiveness of Immunotherapy



Ross RN, Nelson HS, Finegold I. Clin Ther 2000

Meta-analysis – SCIT and asthma



Investigations:

- allergen immunotherapy versus placebo

- 75 randomised, controlled trials

  (33 HDM, 3 HD, 20 pollen, 10 animal dander, 2 cladosp., 1 latex, 6 multiple allergen)

- 1954 – 2002
- 3459 asthmatics

Abramson MJ, et al. Cochrane sys Rev 2003 CD001186 Ia

Significant reduction of symptoms and medication use and BHR

after IT in 75 randomized placebo-controlled trials (1954-2002)

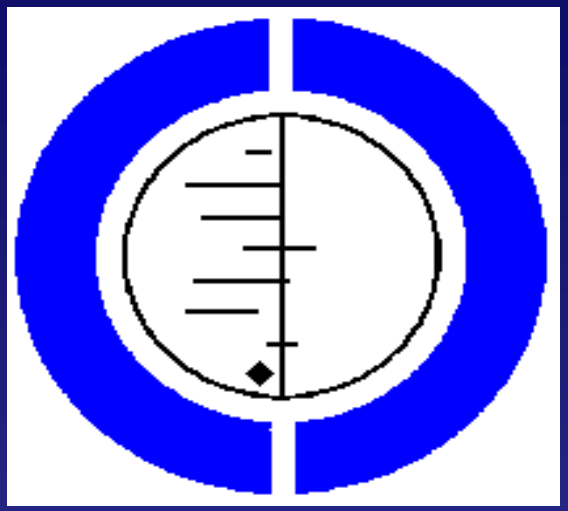
Asthma Symptoms Scores SMD (95% CI)	Asthma Medication Scores SMD (95% CI)	Allergen-Specific BHR SMD (95% CI)
-0.72, (-0.99, -0.33)	-0.90 (-1.13,-0.40	-0.66 (-0.87, -0.45)

Abramson MJ, et al. Cochrane sys Rev 2003 CD001186 Ia

Meta-analysis – SCIT and asthma

Investigations:

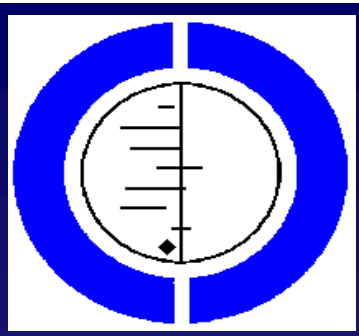
- allergen immunotherapy versus placebo
- house dust mite versus placebo
- pollen versus placebo



- 88 randomised, controlled trials
  (42 HDM, 27 pollen, 10 animal dander, 2 cladosp., 2 latex, 6 multiple allergen)
- 1954 – 2005
- 3792 patients (3459 asthmatics)

Abramson MJ, et al. Cochrane sys Rev 2010, CD001186 Ia

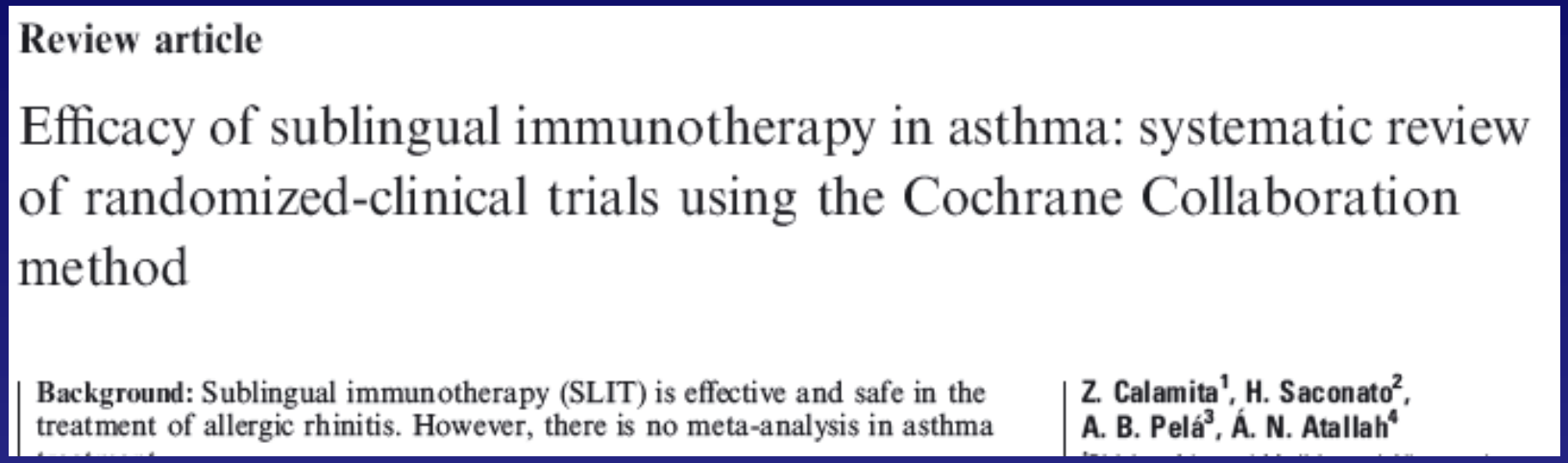
Meta-analysis – SCIT and asthma



Parameter	No. studies	n patients active	n patients placebo	SMD [95%-confidence interval]
Symptom score HDM	12	247	161	-0.48 [-0.96; 0.0]
Medication score HDM	12	242	182	-0.61 [-1.04; -0.18]
Symptom score pollen	18	374	289	-0.61 [-0.87; -0.35]
Medication score pollen	8	182	142	-0.52 [-0.91; -0.13]
Unspecific BHR metacholin	12	248	205	-0.25 [-0.51; 0.00]
Unspecific BHR histamin	4	41	35	-0.55 [-1.37; 0.28]
Lung function: PEF	11	282	242	0.14 [-0.33; 0.61]
Lung function: FEV1	7	110	89	-0.32 [-0.96; 0.31]
Lung function: TGV	2	45	36	0.0 [0.0; 0.0]
Specific BHR HDM	6	98	50	-0.98 [-1.39;-0.58]
Specific BHR pollen	5	104	98	-0.55 [-0.84;-0.27]

Abramson MJ, et al. Cochrane sys Rev 2010, CD001186 Ia

Meta-analysis: SLIT and asthma



Review article

Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method

Background: Sublingual immunotherapy (SLIT) is effective and safe in the treatment of allergic rhinitis. However, there is no meta-analysis in asthma

Z. Calamita[1], H. Saconato[2], A. B. Pelá[3], Á. N. Atallah[4]

Investigations:

- asthmatic symptoms
- asthmatic medication requirements
- 25 randomized-controlled trials
- 1706 patients (adults and children)

Calamita et al.Allergy. 2006 Oct;61(10):1162-72

Meta-analysis: SLIT and asthma

Parameter	No. studies	n patients active	n patients placebo	SMD [95%-confidence interval]
Asthma Symptoms only	9	150	153	-0.38 [-0.79; 0.03]
Allergic symptoms group	10	188	172	-1.18 [-1.93; -0.43]
Reduction of medication use to asthma	6	132	122	-0.91 [-1.94, 0.12]
Reduction of medication use to allergies general	10	250	238	-0.82 [-1.25; -0.39]

Calamita et al.Allergy. 2006 Oct;61(10):1162-72

ASTHMA: Summary of meta-analyses for SCIT and SLIT

Authors (y)	RCTs included (No. of participants)	Symptom scores SMD (95% CI) I^2 (heterogeneity) No. of studies	Medication scores SMD (95% CI) I^2 (heterogeneity) No. of studies	Cochrane Review
		SCIT		
Abramson et al (2003)[16]	75 (3506)	−0.72 (–0.99, –0.44)	−0.80 (–1.13, –0.48)	Yes
	Adults and children	I^2 = 74.1%	I^2 = 65.5%	
		28 Studies	15 Studies	
		SLIT		
Penagos et al (2008)[21]	9 (441)	−1.14 (–2.10, –0.18)	−1.63 (–2.83, –0.44)	No
	Children	I^2 = 94.4%	I^2 = 95.4%	
		9 Studies	7 Studies	
Olaguíbel et al (2005)[22]	5 (193)	−1.42 (–2.51, –0.34)	NR	No
	Children	I^2 = NR		
		6 Studies		
Compalati et al (2009)[23] (only HDM)	9	−0.95 (–1.74, –0.15)	−1.48 (–2.70, –0.26)	No
	Adults and children	I^2 = 93%	I^2 = 96%	

HDM, House dust mite; I^2, I squared (for heterogeneity); *NR*, not reported; *RCT*, randomized controlled trial; *SMD*, standardized mean difference.

JACI 2011;127,1:30-8

Πρόληψη άσθματος

PAT Study ***(Preventive Allergy Treatment)*** **: 6 χώρες**

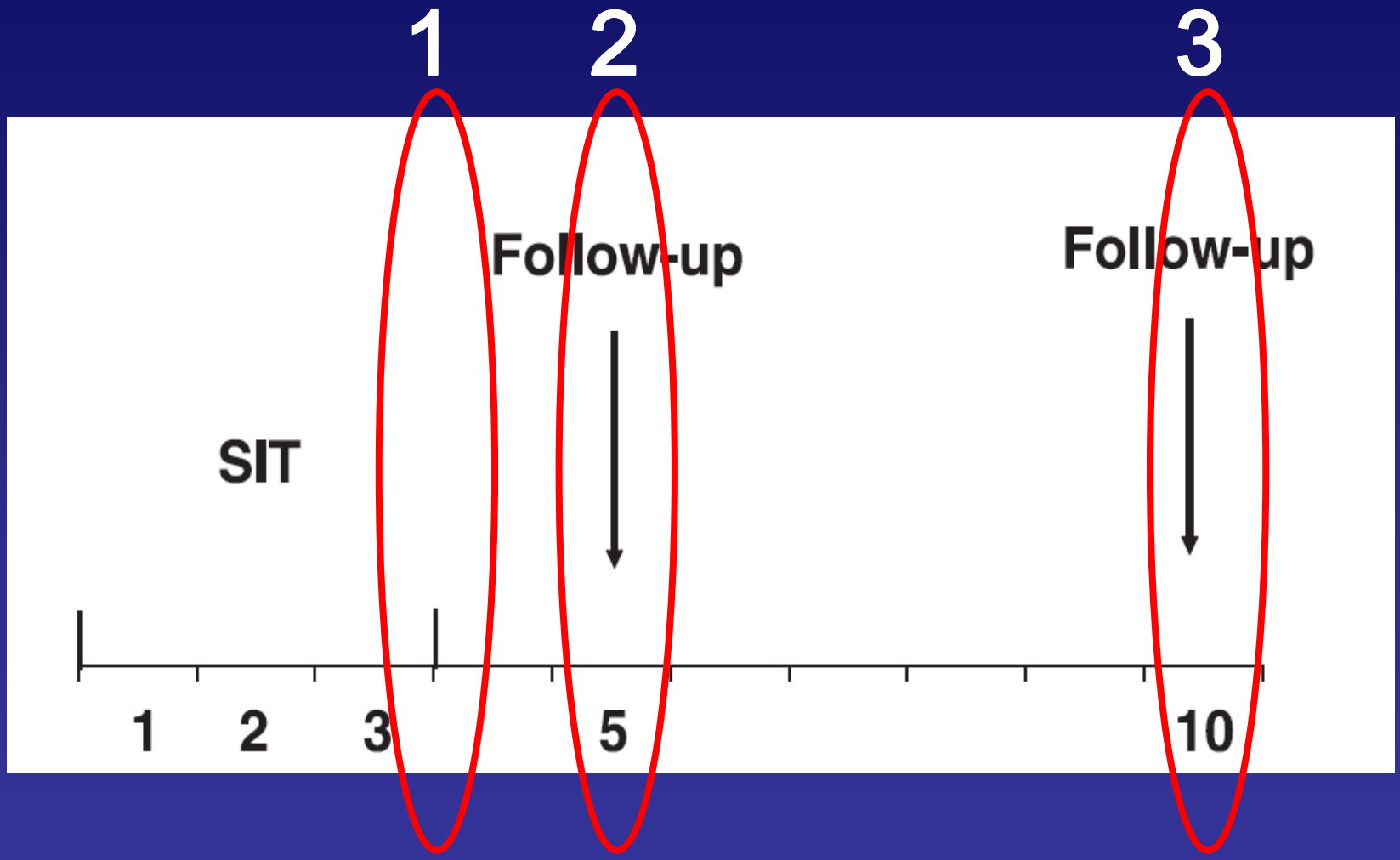
208 παιδιά (6-14) σημύδα και/ή γρασίδι

Οφθαλμική πρόκληση (+), SPT(+)

Τυχαιοποιημένη: SCIT - φαρμακοθεραπεία

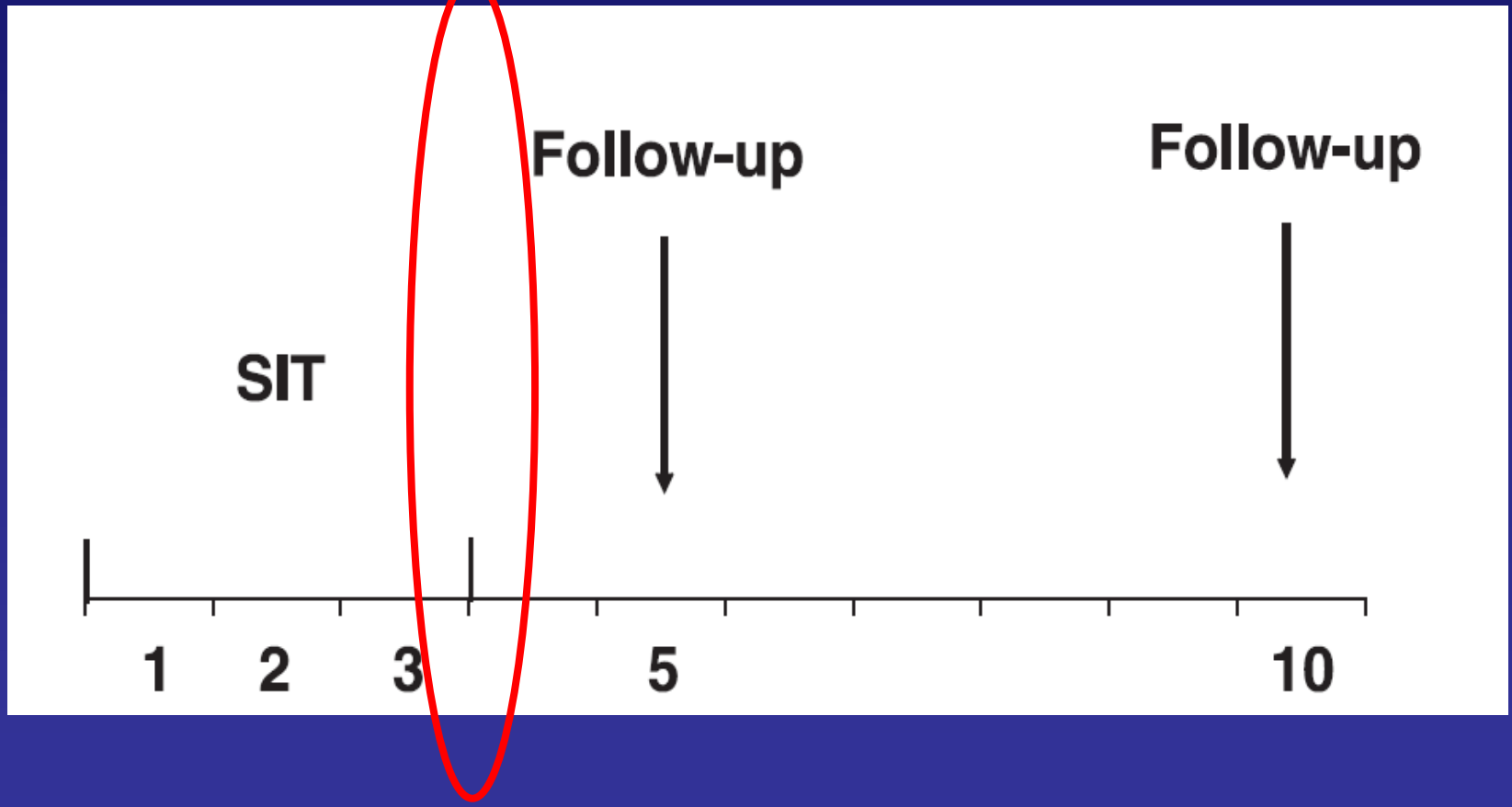
Möller C, et al. JACI,2002; 109: 251

PAT Study period



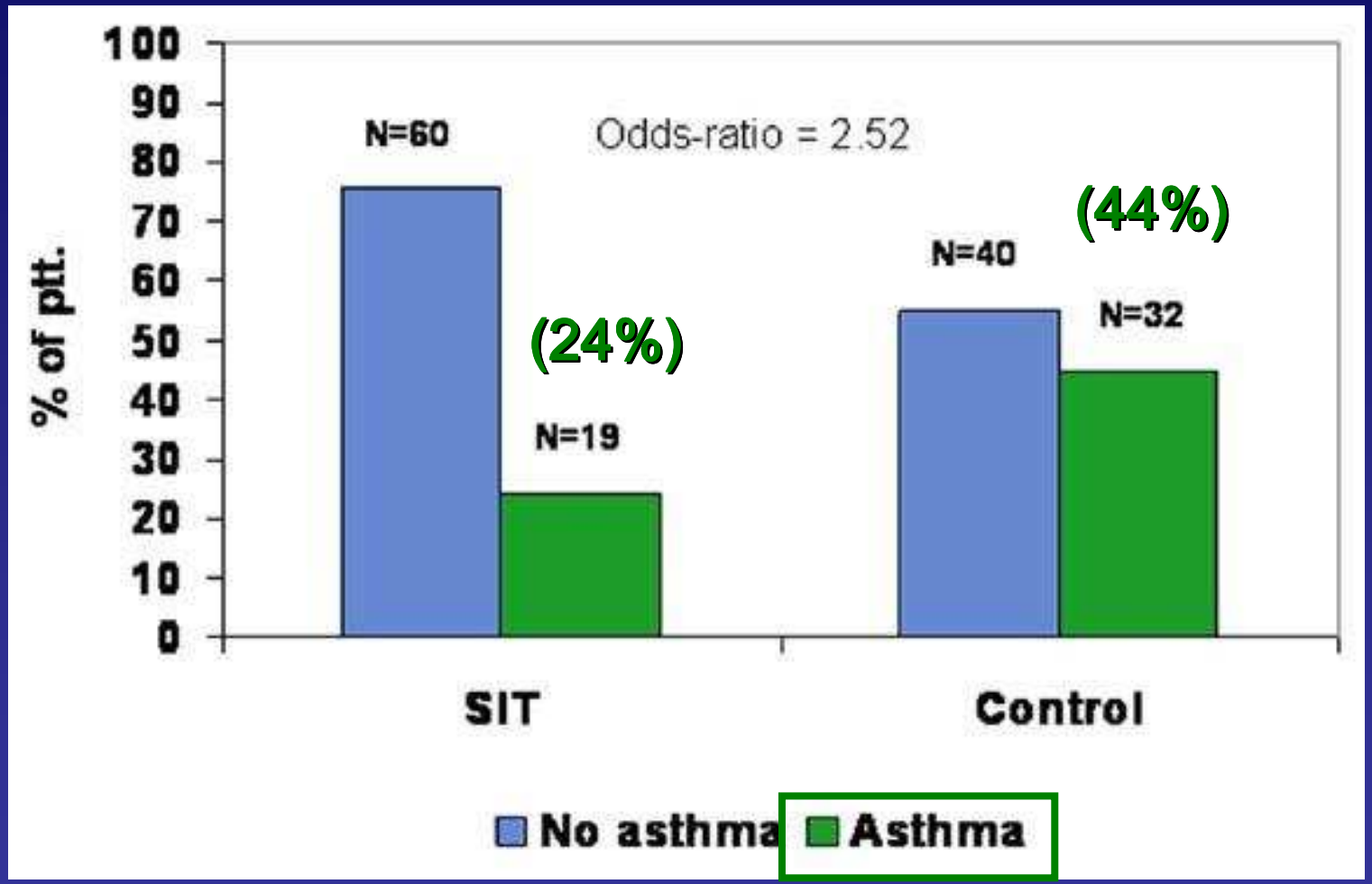
Jacobsen L, et al. Allergy, 2007; 62: 943

PAT Study period



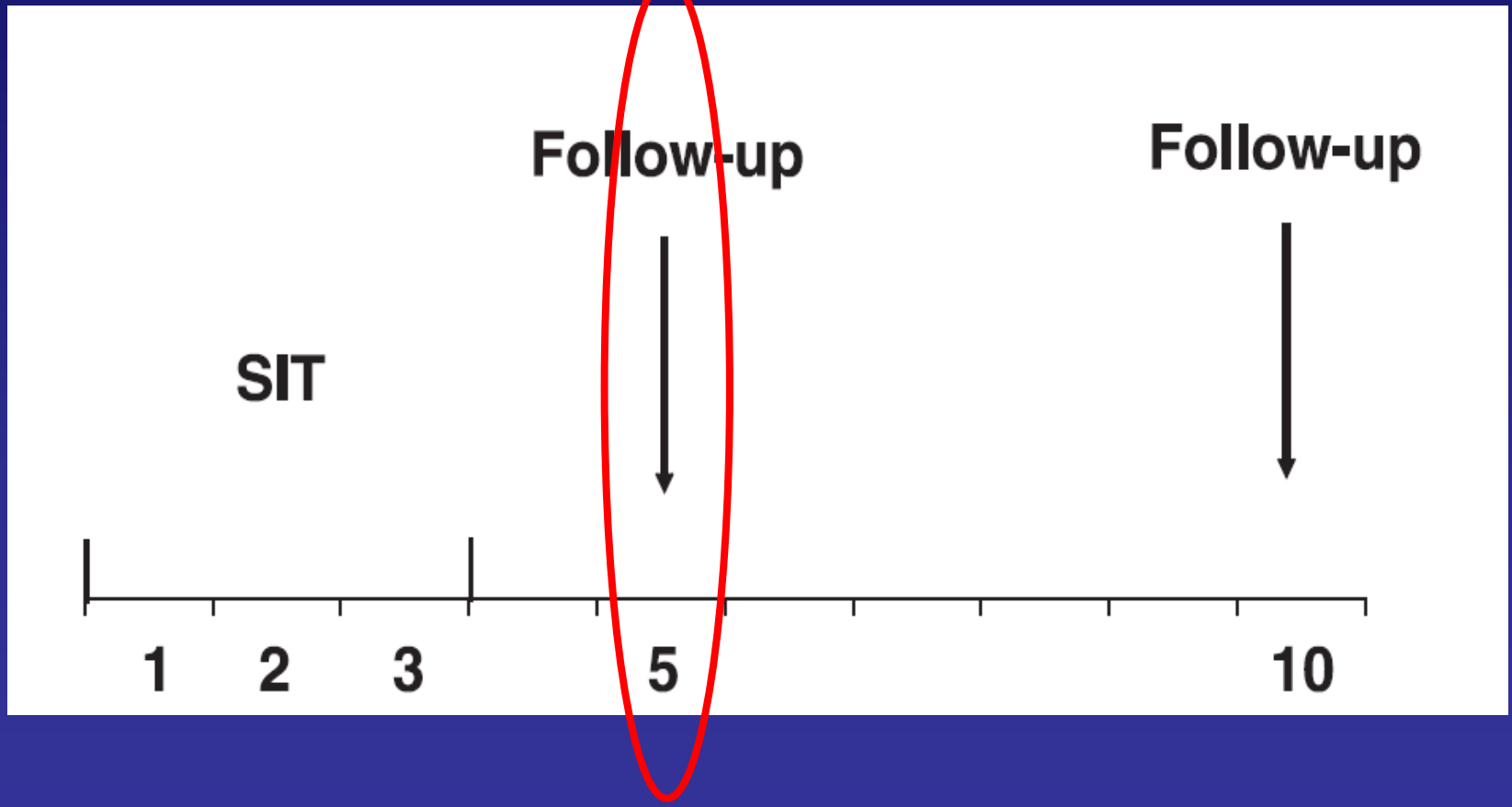
Jacobsen L, et al. Allergy, 2007; 62: 943

Πρόληψη άσθματος



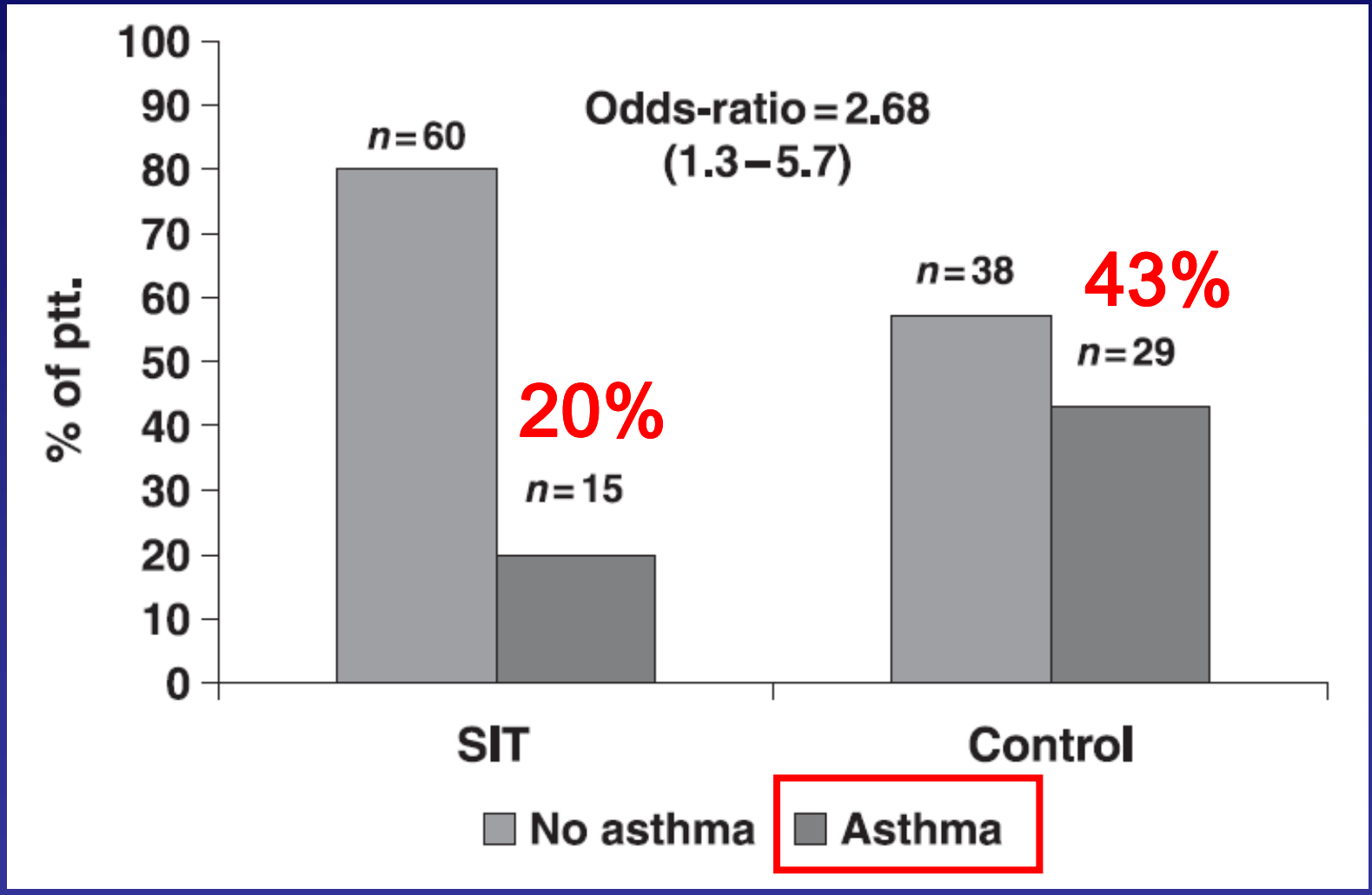
Möller C, et al. JACI,2002; 109: 251

PAT Study period



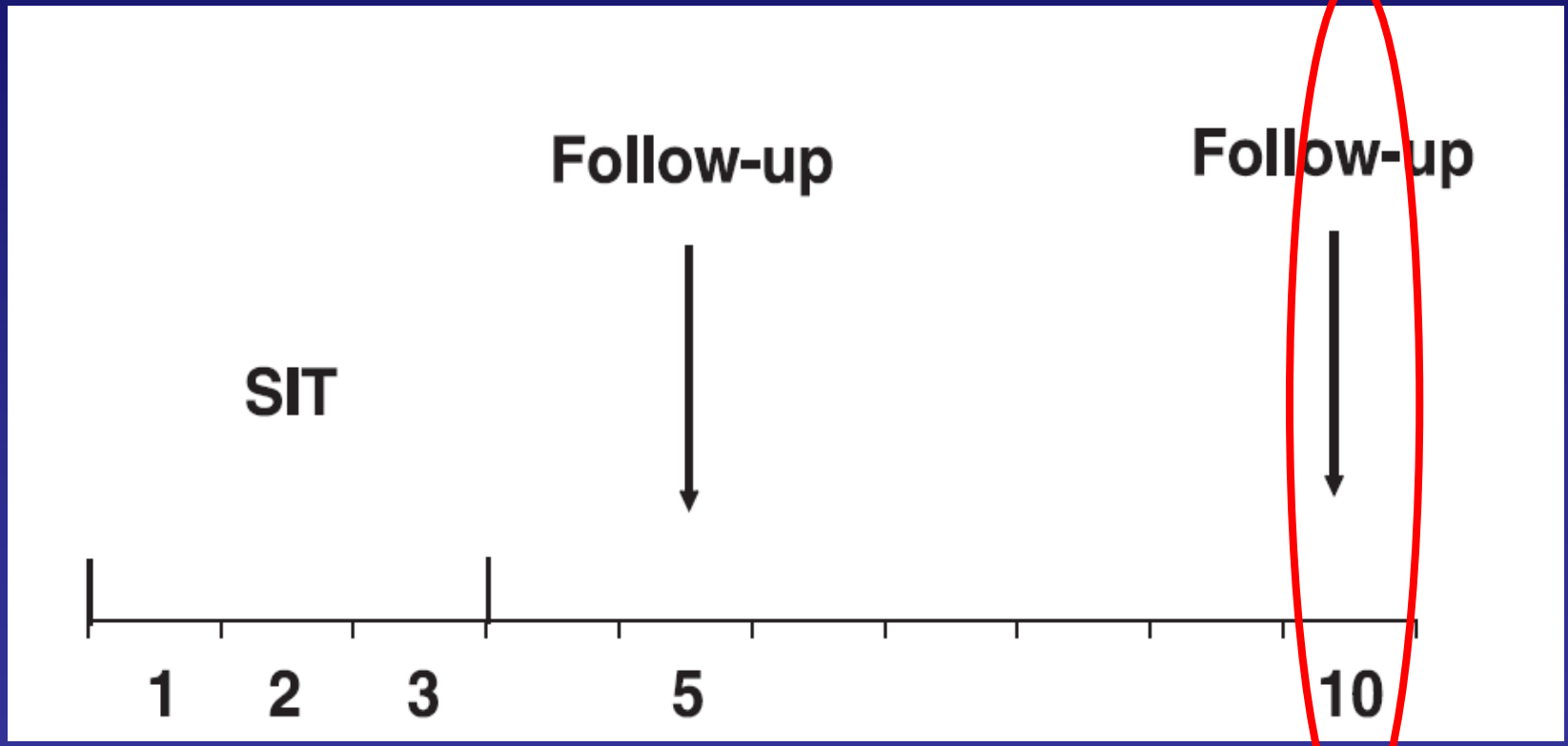
Jacobsen L, et al. Allergy, 2007; 62: 943

The percentage of children with and without asthma 2 years after termination of immunotherapy



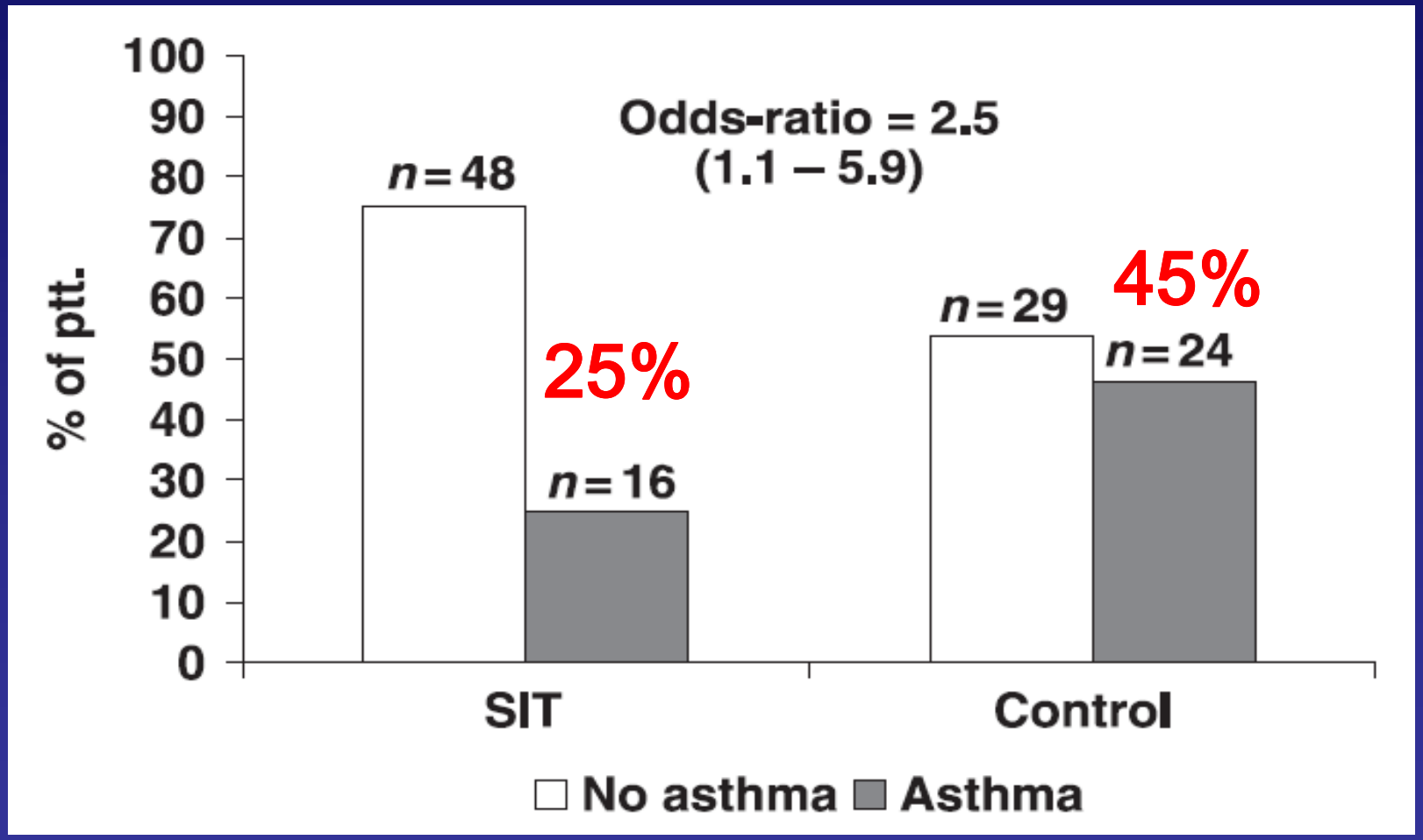
Niggemann B, et al. Allergy, 2006; 61: 855

PAT Study period



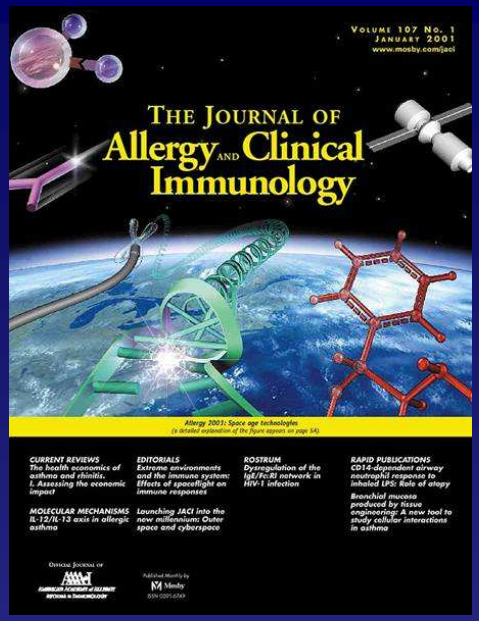
Jacobsen L, et al. Allergy, 2007; 62: 943

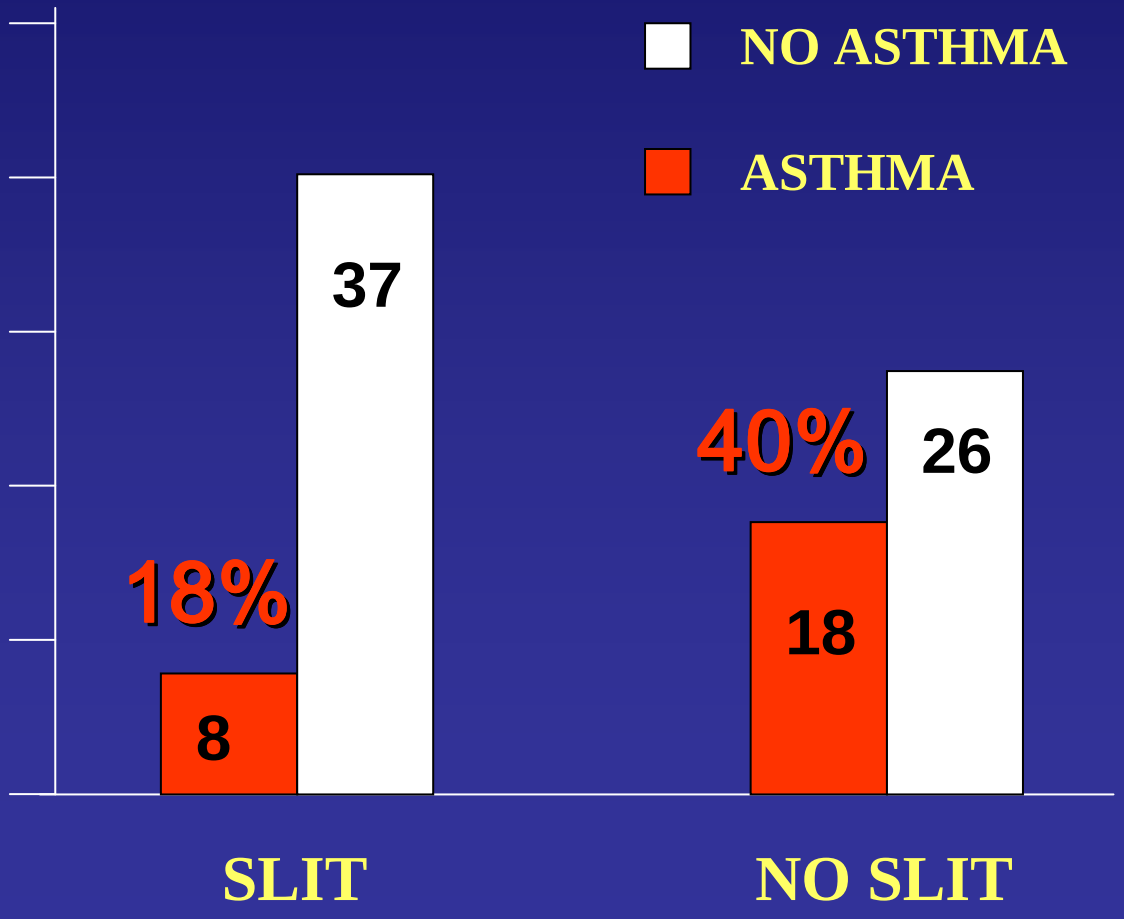
The percentage of children with and without asthma 7 years after termination (10-year follow-up) of specific immunotherapy



Jacobsen L, et al. Allergy, 2007; 62: 943

SLIT reduces the development of asthma in children with allergic rhinitis.
Novembre E. et al, JACI 2004





79 children
Allergic rhinitis only
Follow-up: 3 yrs

Πρόληψη άσθματος και νέων ευαισθησιών

28 παιδιά (6-14): αλλ. ρινίτιδα: γρασίδι

(14) 3ετή SCIT (14) φάρμακα

6 έτη μετά τη διακοπή (13 – 10)

Άσθμα: 23% των SCIT - 70% των άνευ SCIT

Νέες ευαισθησίες: 61% SCIT - 100% άνευ SCIT

12 έτη μετά τη διακοπή (12 – 10)

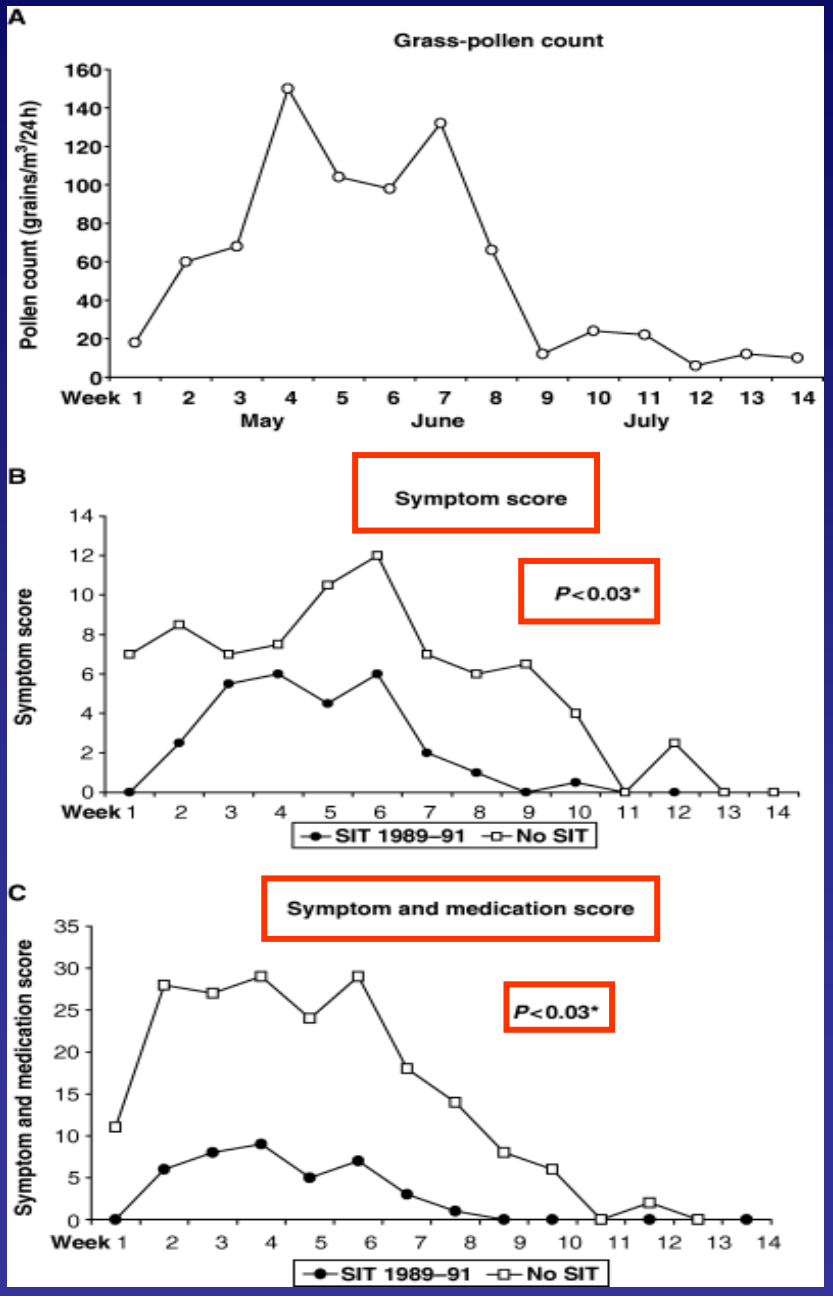
Άσθμα: 30% των SCIT - 70% των άνευ SCIT

Νέες ευαισθησίες: 61% SCIT - 100% άνευ SCIT

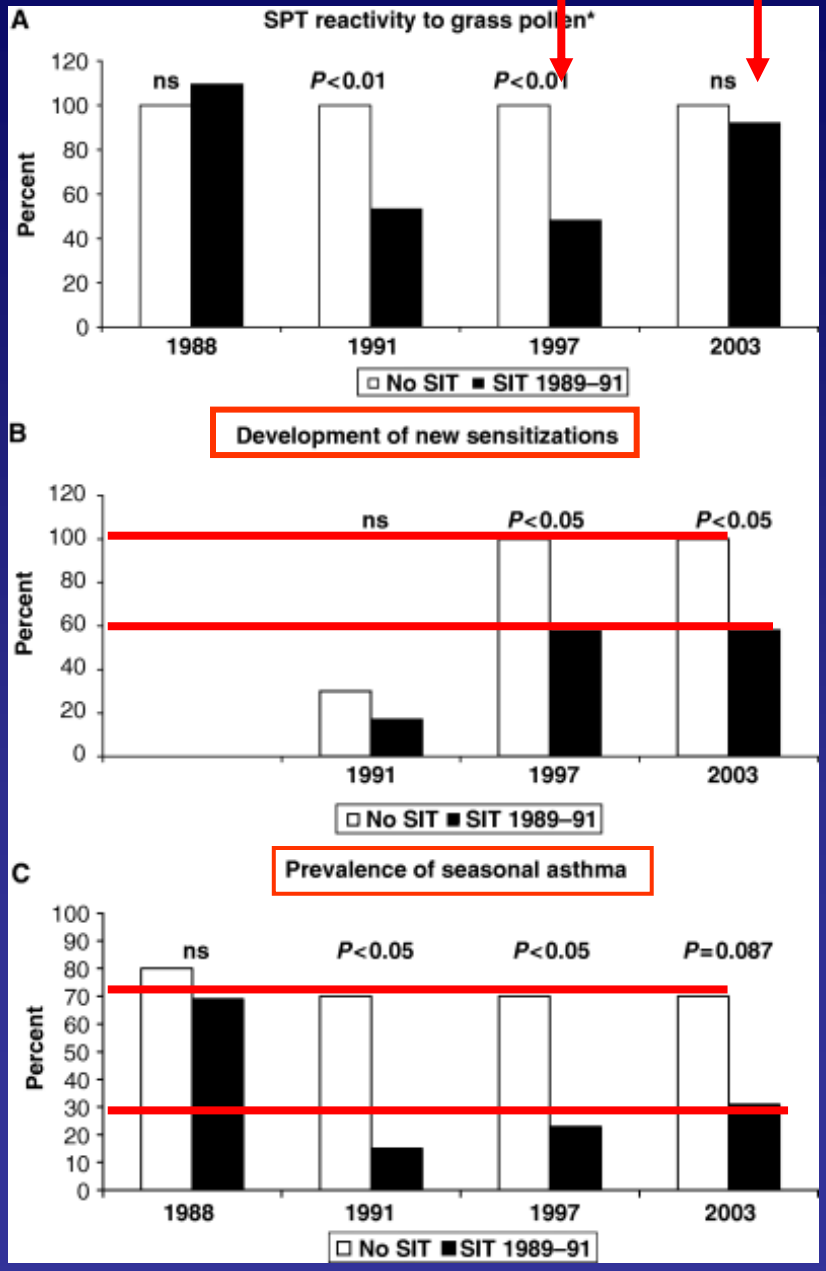
Eng PA, et al. Allergy, 2002; 57: 306

Eng PA, et al. Allergy, 2006; 61: 198

12 έτη μετά [12 - 10]



6 έτη 12 έτη



Preventive effect of immunotherapy on the development of new allergen sensitizations in monosensitized patients

Study	Age (yr; mean)	Immunotherapy Method and Number of Patients in Each Treatment Group	Immunotherapy (% of Patients with New Allergen Sensitizations)	Control (% of Patients with New Allergen Sensitizations)	*p* Value
Des Roches 1997	4–6 (5) 3–5 (4)	SCIT, 22 Control, 22	54	100	0.001
Purello-D'Ambrosio 2001	Adults and pediatric	SCIT, 7182 Control,1214	23	68	<0.00001
Pajno 2001	6–8 (7.14) 5–7 (6.38)	SCIT, 75 Control, 63	24.6	66.7	<0.0002
Marogna 2004	5–60 (22.8) 5–58 (21.5)	**SLIT**, 319 Control,192	5.9	38	0.01

Cox L. Allergy Asthma Proc 2008 29:1

Διάρκεια Ανοσοθεραπείας

- 40 ασθενείς με αλλ. άσθμα ακάρεα
- 12-96 μήνες SCIT

- Μέσα στα 3 επόμενα έτη 55% επανεμφάνισαν συμπτώματα

- A) SCIT <36 μήνες 62%
- B) SCIT >36 μήνες 48% (p<0.04)

Del Roches, et al. Allergy, 1996; 51:430-3

According to the update AIPP

(Allergen Immunotherapy Practice Parameters)

In asthmatic patients, "immunotherapy is indicated in individuals who experience symptoms of asthma after natural exposure to aeroallergens AND one of the following:

- Poor response to pharmacotherapy, allergen avoidance, or both;
- Unacceptable adverse effects of medication;
- Wish to reduce or avoid long-term pharmacotherapy;
- Co-existing allergic rhinitis and allergic asthma."

JACI 2011;127,1:30-8

Indications for specific immunotherapy (SLIT)

1) Patients with rhinitis, conjunctivitis, and/or **asthma** caused by **allergy to pollens or house dust mites**
2) Patients who are inadequately controlled with conventional pharmacotherapy
3) Patients who have had systemic reactions during specific immunotherapy by injection
4) Patients who have compliance problems with or refuse immunotherapy by injection

JACI 2011;127,1:30-8

Contraindications for specific immunotherapy

- Malignant diseases
- Autoimmune diseases
- Current therapy with beta blockers
- Pregnancy at the start of immunotherapy
- **Asthma patients with FEV1 below 70% under treatment, or uncontrolled asthma**

Zuberbier T et al. Allergy 2010, 65:1525–1530

ΚΡΙΤΗΡΙΑ

Γίνεται σε αλλεργικούς !!!!!!!!!!!!!!!!!

Η ανοσοθεραπεία είναι αποτελεσματική όταν:

1. **Χρησιμοποιούνται καλά τυποποιημένα σκευάσματα**
2. **Προβλεπόμενη δόση**

   SCIT: 5-20μg μείζον αλλεργιογόνο/μήνα
   SLIT:15-25μg μείζον αλλεργιογόνο/ημέρα
3. **Δεν χρησιμοποιούνται πολλά αλλεργιογόνα μαζί**
4. **Μύκητες μόνο σε καλά τεκμηριωμένα περιστατικά, όχι σε μίγματα (*πρωτεάσες*)**

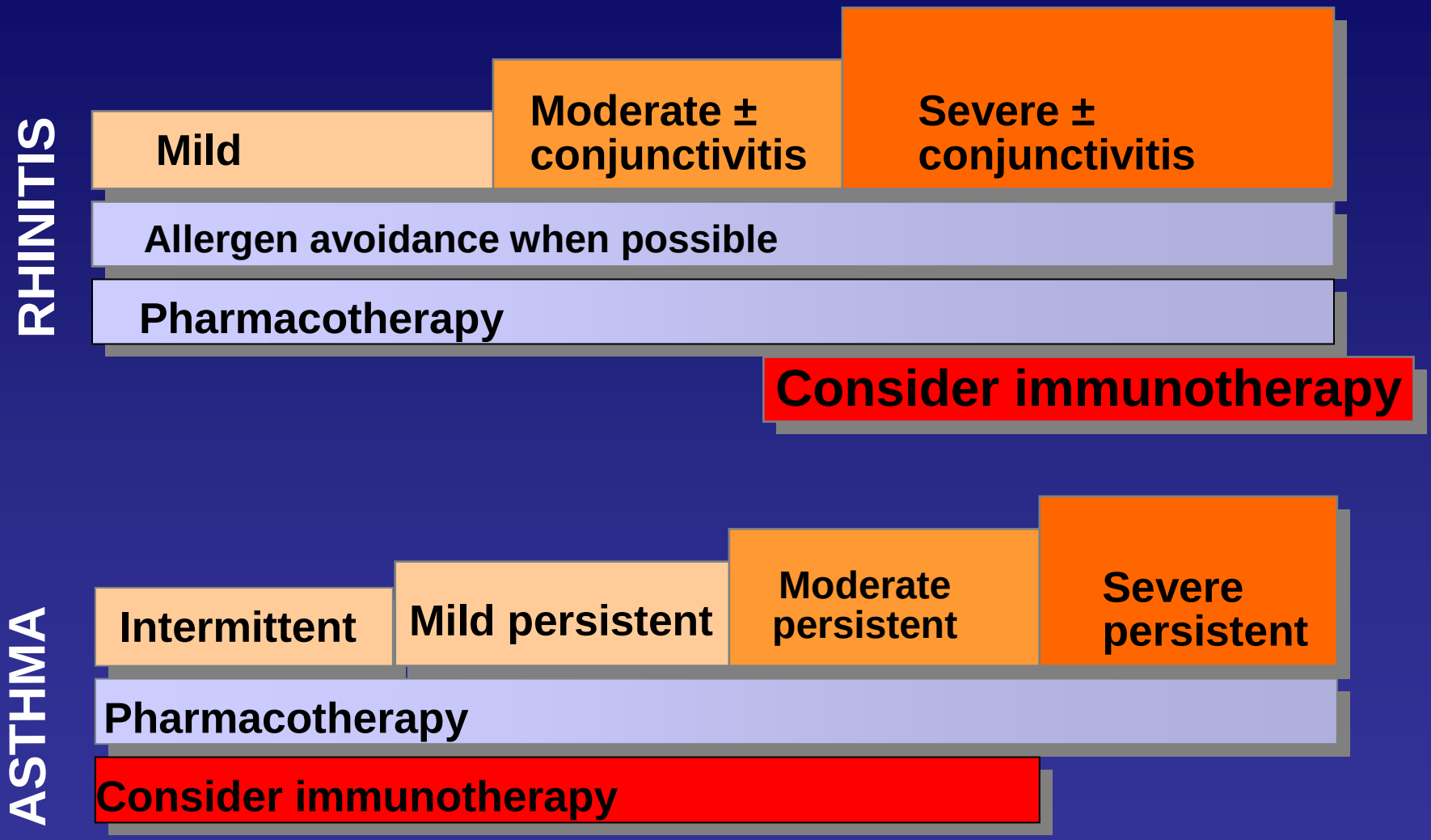
ΣΥΜΠΕΡΑΣΜΑΤΑ

Η ανοσοθεραπεία στο άσθμα υπερέχει της φαρμακοθεραπείας διότι

1. **Έχει αποτελεσματικότητα που διαρκεί και μετά τη διακοπή της**
2. **Προλαμβάνει τη κλινική συμπτωματολογία από άλλα όργανα**
3. **Προλαμβάνει νέες ευαισθητοποιήσεις**

Passalacqua G, et al. JACI, 2007; 119: 881.

When to Consider Immunotherapy



Comparison of the systematic reviews of sublingual and subcutaneous immunotherapy

Immunotherapy Route	Asthma Symptoms Scores SMD (95% CI)	Asthma Medication Scores SMD (95% CI)	Allergen-Specific BHR SMD (95% CI)
Subcutaneous *Ambramson Cochrane 2003*	-0.72, (-0.99, -0.33)	-0.90 (-1.13,-0.40)	-0.66 (-0.87, -0.45)
Sublingual *Calamita Cochrane 2006*	-0.38 (-0.79, 0.03)	-0.91 (-1.94, 0.12)	"no significant improvement favoring SLIT"

BHR: *bronchial hyperreactivity*
CI *: confidence interval;*
SMD: *standarized mean difference.*

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Factors to Consider When Prescribing Immunotherapy

- Effectiveness of medications and avoidance measures
- Side effects/costs of medications vs. immunotherapy
- Possible special benefit in children as preventative therapy for asthma
- Patient adherence to medication and recommendations