



**XVIII Congresso Nazionale
Società Italiana di Pediatria
Preventiva e Sociale**

**UN'INFANZIA DA DIFENDERE:
IL RUOLO DEL PEDIATRA**

Con il patrocinio del Ministero della Salute



**28 - 31 Ottobre 2006
Hotel President - Lecce**

ALLERGOLOGIA E BRONCOPNEUMOLOGIA

**L'immunoterapia specifica
dell'asma**

Alessandro Fiocchi (Milano)



L'immunoterapia specifica dell'asma

- Storia naturale della malattia asmatica
- Può l'immunoterapia specifica dell'asma modificare questa storia?
 - A che età possiamo cominciare?



In puero homo



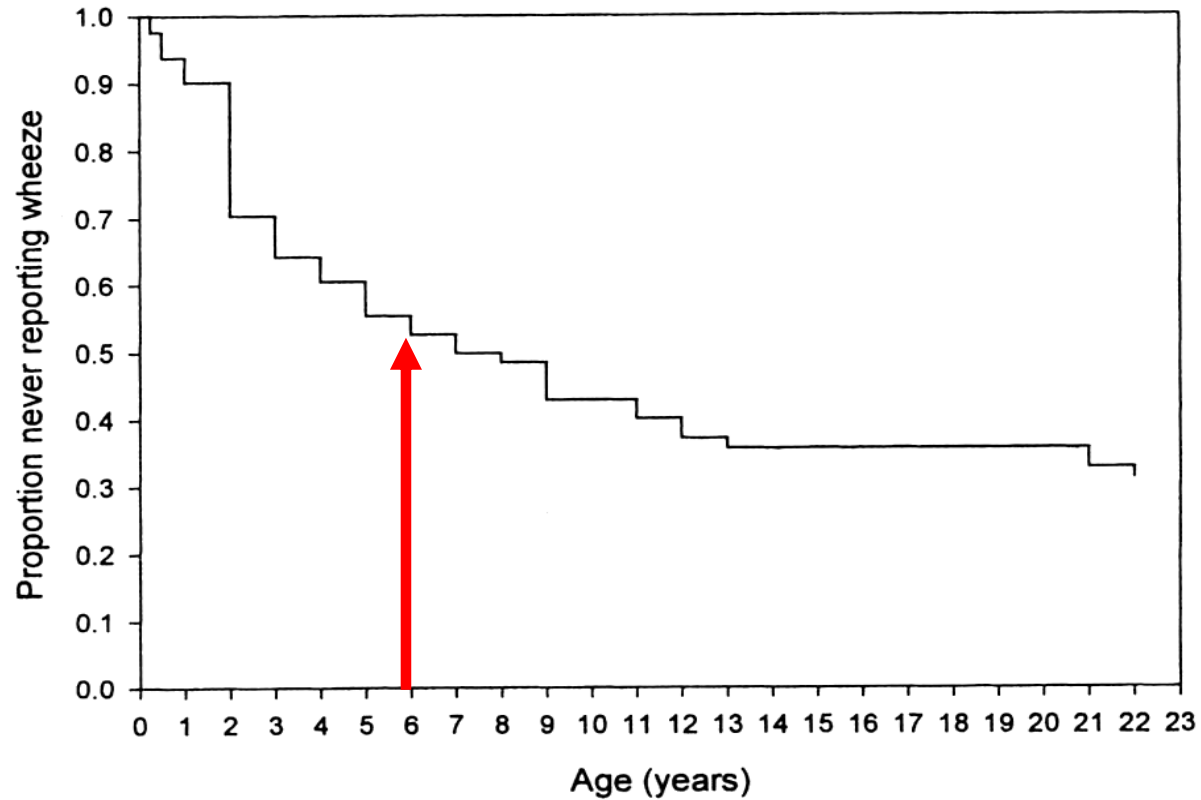


In puero homo In paediatric asthma adult asthma?

- a. Asthma can begin in the perinatal period.
- b. An infant can be a “true” asthmatic
- c. Asthma tracks from infancy to childhood
- d. Asthma tracks from childhood to adolescence
- e. Asthma tracks from childhood to adulthood
- f. Childhood asthma can anticipate COPD



Onset of asthma before the sixth year in 80% of cases





Asthma does not remit during adolescence

Mean age \pm SD at the onset of puberty: 12.2 \pm 1 years

1. NW - No wheezing: 51%
2. IUW - Infrequent unremitting wheezing: 5%
3. IRW - Infrequent remitting wheezing: 12%
4. UA - Unremitting asthma: 12%
5. RA - Remitting asthma: 9%
6. IW - Wheezing attacks only after puberty (incident wheezing): 11%

Guerra S. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med.* 2004; 170:78-8



Asthma does not remit during adolescence

	NW	IUW	IRW	UA	RA	IW	P
Female %	56.6	56.4	46.7	44.3	33.3	66.3	0.0003
Puberty age	12.17	11.74	12.34	11.95	12.70	11.79	<0.0001
Maternal smoking pregnancy	13.4%	18.4%	14.6%	11.7%	20.9%	19.0%	ns
Smoke in home	28.6%	46.2%	34.1%	28.9%	42.0%	49.4%	0.002
Active smoking	14.5%	11.1%	11.3%	15.9%	8.3%	26.3%	0.129

Guerra S. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med.* 2004; 170:78-83

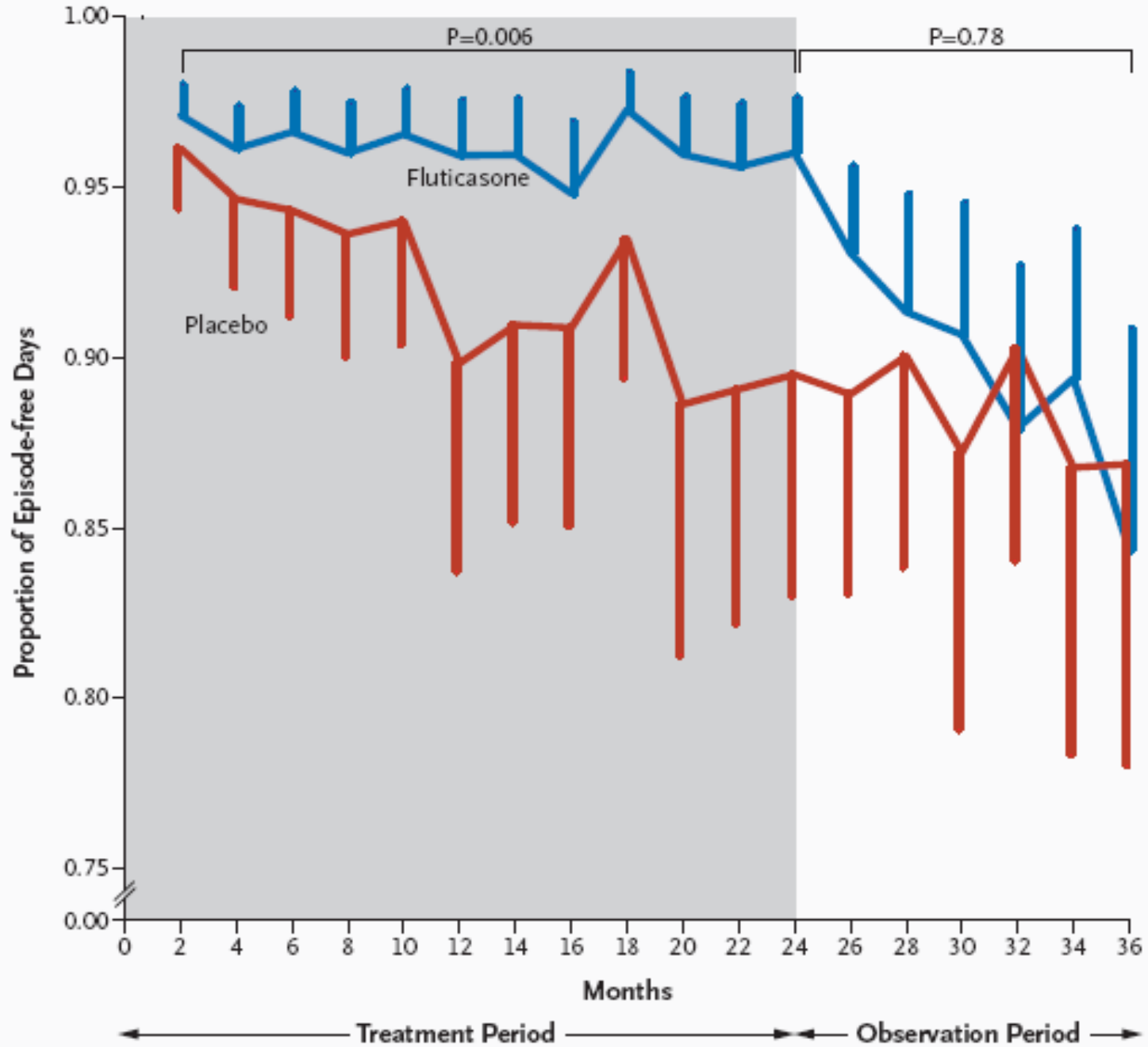


Allergy factors associated with unremitting asthma

SPT+	NW	IRW	IUW	RA	UA	P
6 years	26.4	29.5	53.8	54.0	73.2	0.0001
11 years	42.8	50.0	75.8	62.7	84.8	0.0001
16 years	63.5	61.9	85.2	80.0	95.5	0.0001



Guerra S. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med.* 2004; 170:78-85





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Original Article

Standards for practical allergen-specific immunotherapy

Alvarez-Cuesta, J. Bousquet, G. W. Canonica, S. R. Durham, H.-J. Malling, E. Valovirta

EAACI, Immunotherapy Task Force

Definition of allergen-specific immunotherapy

is the practice of administering gradually increasing quantities of an allergen extract or product to an allergic subject to ameliorate the symptoms associated with the disease. It is a subsequent exposure to the causative allergen.

It induces clinical and immunologic tolerance, has long-term efficacy and may prevent the progression of allergic disease. Allergen-specific immunotherapy also improves the quality of life of allergic patients.

This definition is based on category I evidence.



Treatment strategy

Available treatments for allergic diseases include:

1. Allergen avoidance
2. Pharmacotherapy
3. SIT
4. Patient education





Although many drugs are effective and without significant side-effects, drugs represent a symptomatic treatment,.....

.. immunotherapy represents the only treatment that might alter the natural course of the disease

Moller C. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PATstudy). *J Allergy Clin Immunol* 2002;109:251–6

Novembre E. Coseasonal sublingual IT reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;114:851–7

Durham SR. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468–475.



DRUGS

SIT

Prompt action

YES

NO

Preventive effect

NO

YES

Side effects

YES

NO

Cost

LOW

HIGH

Long lasting

NO

YES



Subcutaneous immunotherapy

Efficacy using inhalant allergens



75 double-blind, placebo-controlled studies published from 1980 to 2005 (15 out of the 75 studies included children)

clinically relevant decreases in symptom-medication scores

EAACI - IT task force. Standards for practical allergen-specific immunotherapy.

Allergy 2006; 61 (Suppl. 82): 1–20



Subcutaneous immunotherapy

Long-lasting effect



Long-term efficacy of immunotherapy following a double-blind, placebo-controlled withdrawal of the treatment

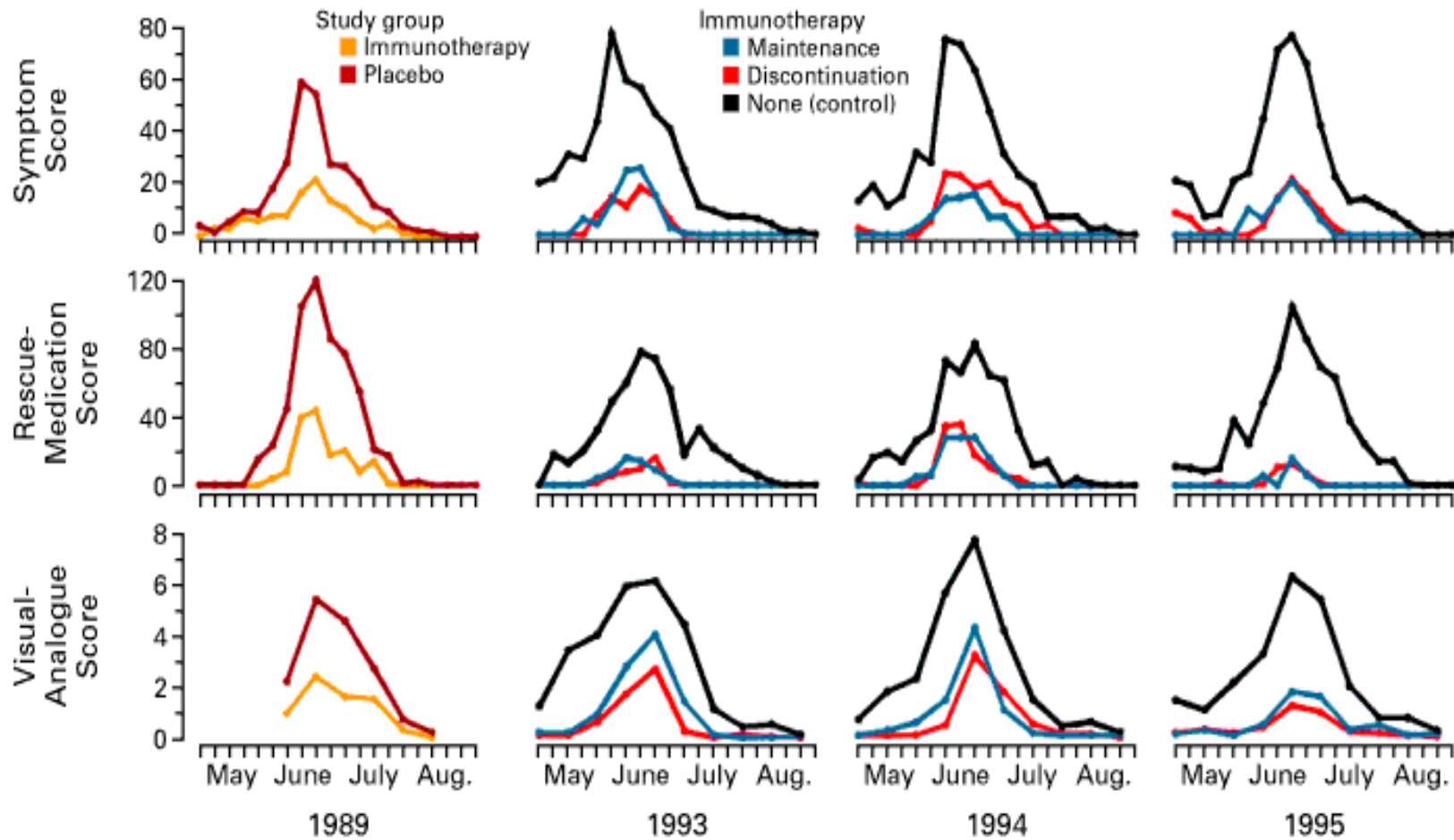
Durham SR. Long-term clinical efficacy of grass pollen immunotherapy. *N Engl J Med* 1999;341:468–75

The category of evidence for long-term efficacy and preventive capacity is Ib.

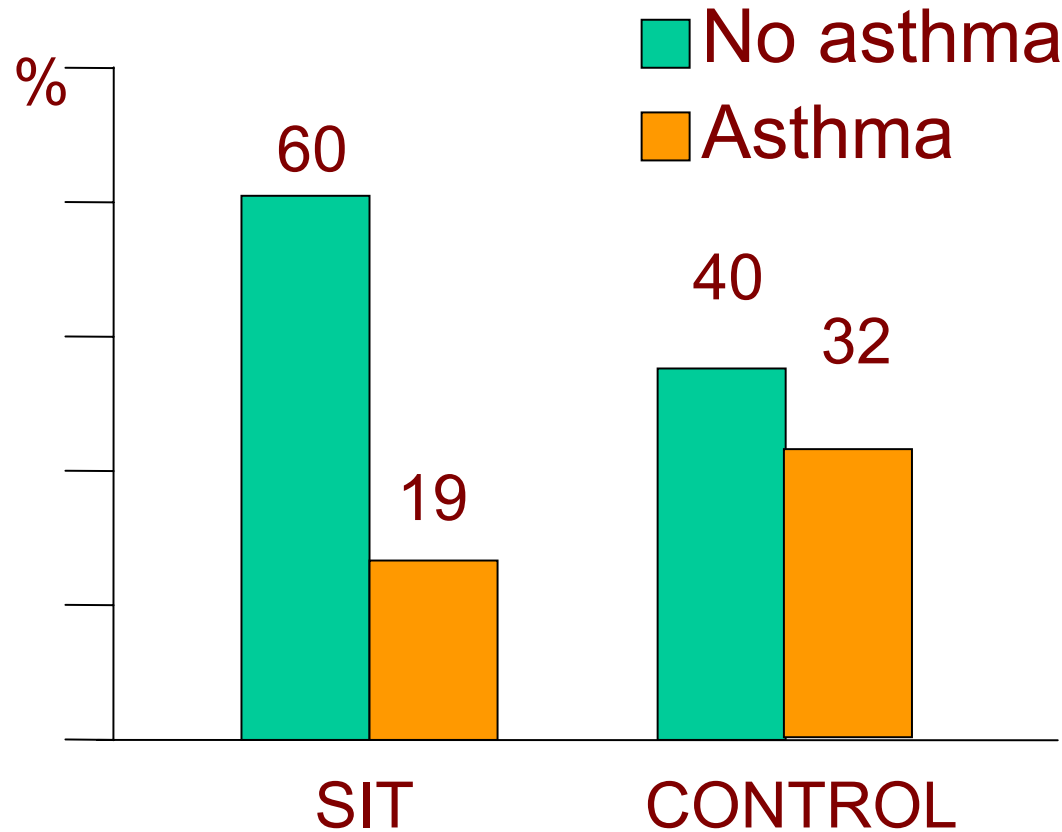
EAACI - IT task force. Standards for practical allergen-specific immunotherapy



Long-term clinical efficacy of grass pollen immunotherapy.



Development of asthma in children with allergic rhinitis



205 children with rhinitis

age: 6-14 yrs

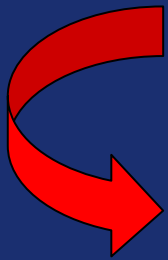
grass or birch allergy

3 yrs immunotherapy



Long-term prevention of asthma in children

The children were evaluated 2 years after termination of a 3-year course of SIT.



Children who received SIT were 2.68 times more likely to remain asthma free than were control children



Twelve-year follow-up after grass pollen immunotherapy in childhood

22 patients with previous SIT – reduced:

Total hay fever symptom score ($P < 0.03$)

use of medication ($P < 0.05$)

combined symptom and medication score ($P < 0.03$)

percentage of new sensitization in patients (58% vs. 100%, $P < 0.05$)

tendency for lower prevalence of seasonal asthma in the post-SIT group ($P = 0.08$).



Subcutaneous immunotherapy reduces the development of new sensitizations

New sensitizations after 3 years: 55% SIT group vs 100% control group.
Des Roches et al, JACI 1997

New sensitizations after 3 years: 25% SIT group vs 67% control group.
Pajno et al, Clin Exp Allergy 2001

New sensitizations after 4 years: 23% SIT group vs 68% control group.
Purello D'Ambrosio et al, Clin Exp Allergy 2001.



Sublingual-swallow immunotherapy

Evidence for clinical efficacy in asthma: Ib

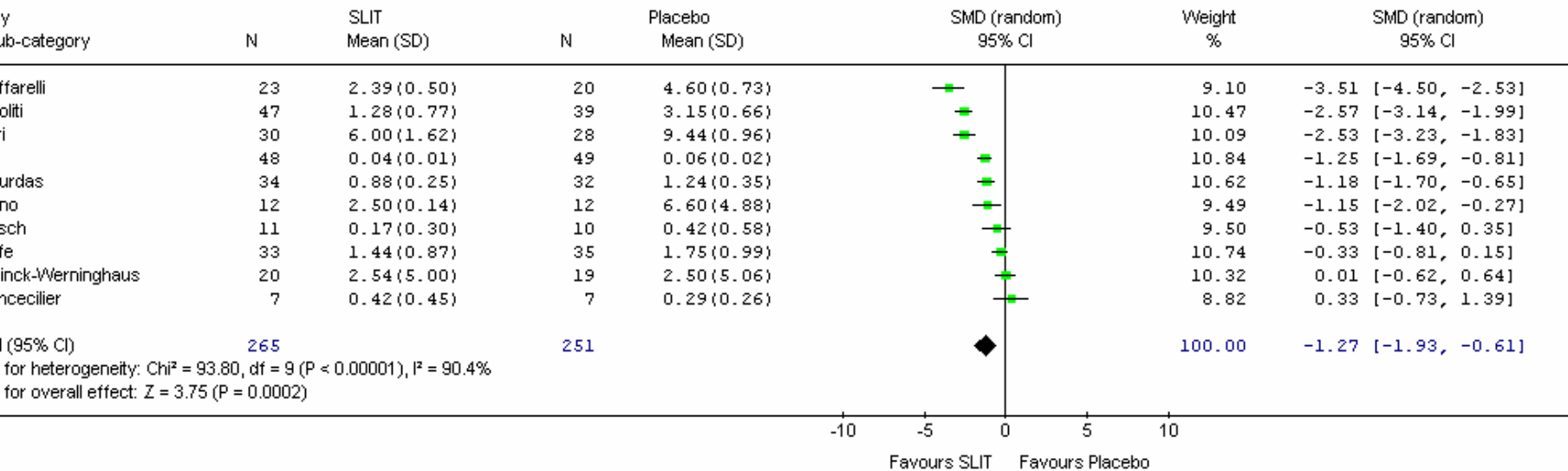
Indications:

- Patients with allergic rhinoconjunctivitis and asthma
- Patients sensitive to birch, grasses, cypress, olive, Parietaria and house dust mites
- Patients insufficiently controlled by antiallergic drugs
- Patients with systemic reactions after subcutaneous immunotherapy.
- Patients refusing injection immunotherapy.

Meta-analysis of the efficacy of sublingual immunotherapy in allergic asthma in pediatric patients, 3 to 18 years of age.

M Penagos, G Passalacqua, E Compalati, C Baena-Cagnani, S Orozco, A Pedroza GW Canonica

Review: Efficacy of Sublingual Immunotherapy in the treatment of asthma in children. Meta-analysis of randomized controlled trials.
 Comparison: 02 Bronchial score asthma
 Outcome: 01 Bronchial score asthma

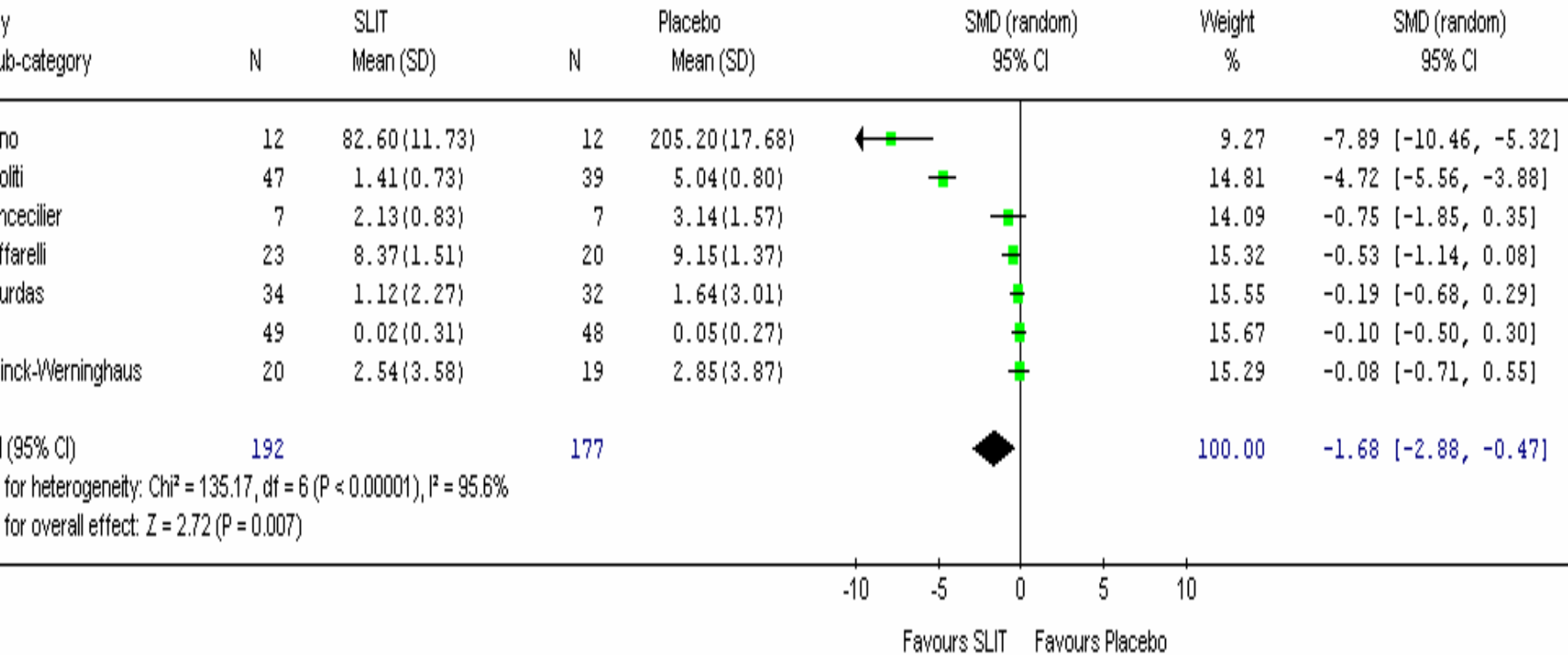


Penagos M. Meta-analysis of the efficacy of sublingual immunotherapy in allergic asthma in pediatric patients, 3 to 18 years of age. Ann Allergy Asthma Immunol 2006; 97, 137-

Meta-analysis of the efficacy of sublingual immunotherapy in allergic asthma in pediatric patients, 3 to 18 years of age.

M Penagos, G Passalacqua, E Compalati, C Baena-Cagnani, S Orozco, A Pedroza GW Canonica

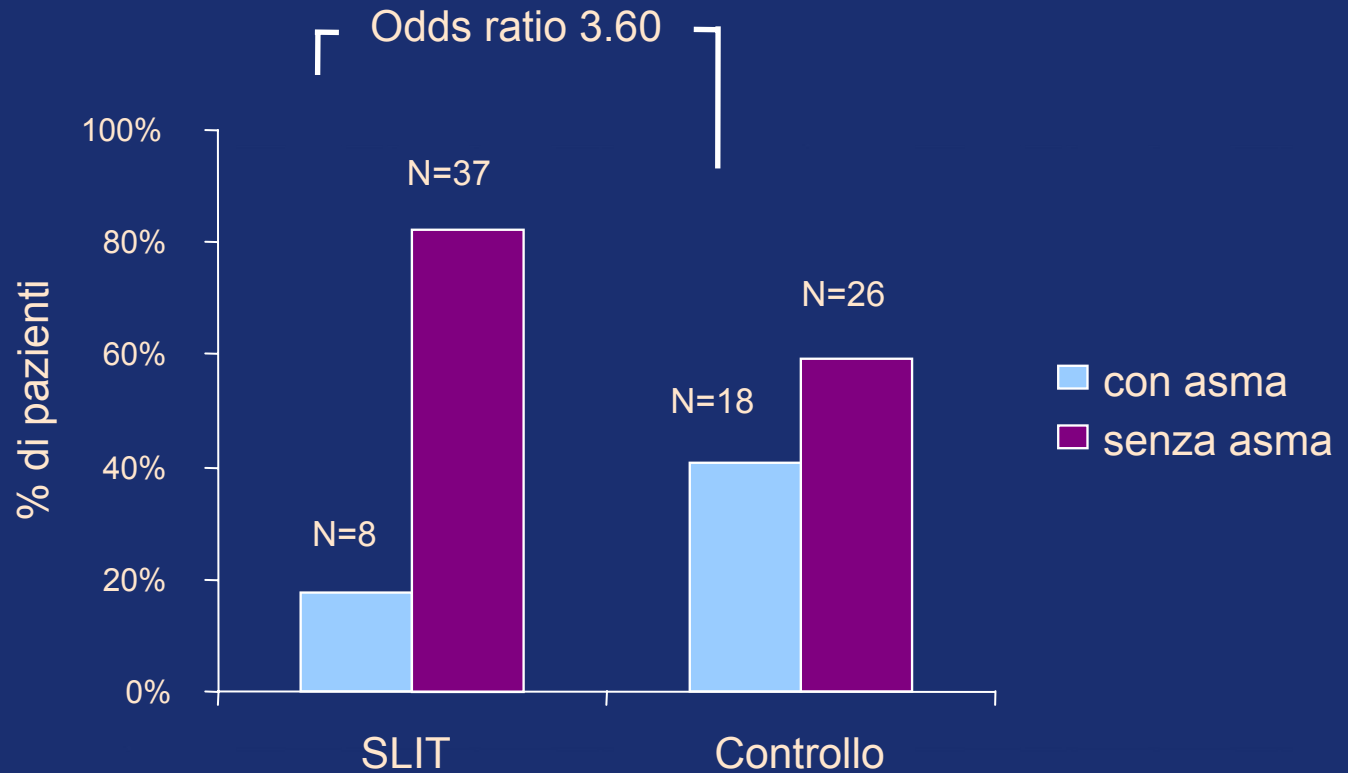
Review: Efficacy of Sublingual Immunotherapy in the treatment of asthma in children. Meta-analysis of randomized controlled trials.
 Comparison: 01 Medication score asthma
 Outcome: 01 Medication score asthma





La SLIT riduce il rischio di sviluppare asma

Pazienti con rinite allergica. Follow-up a 3 anni





Long-lasting effect of SLIT

An open prospective study

35 treated children (3-17) - mean 8 yrs

25 untreated children (4-17) - mean 9 yrs

Allergic to mites

Asthma and/or rhinitis

SLIT for 4-5 years (ALK-Abellò)

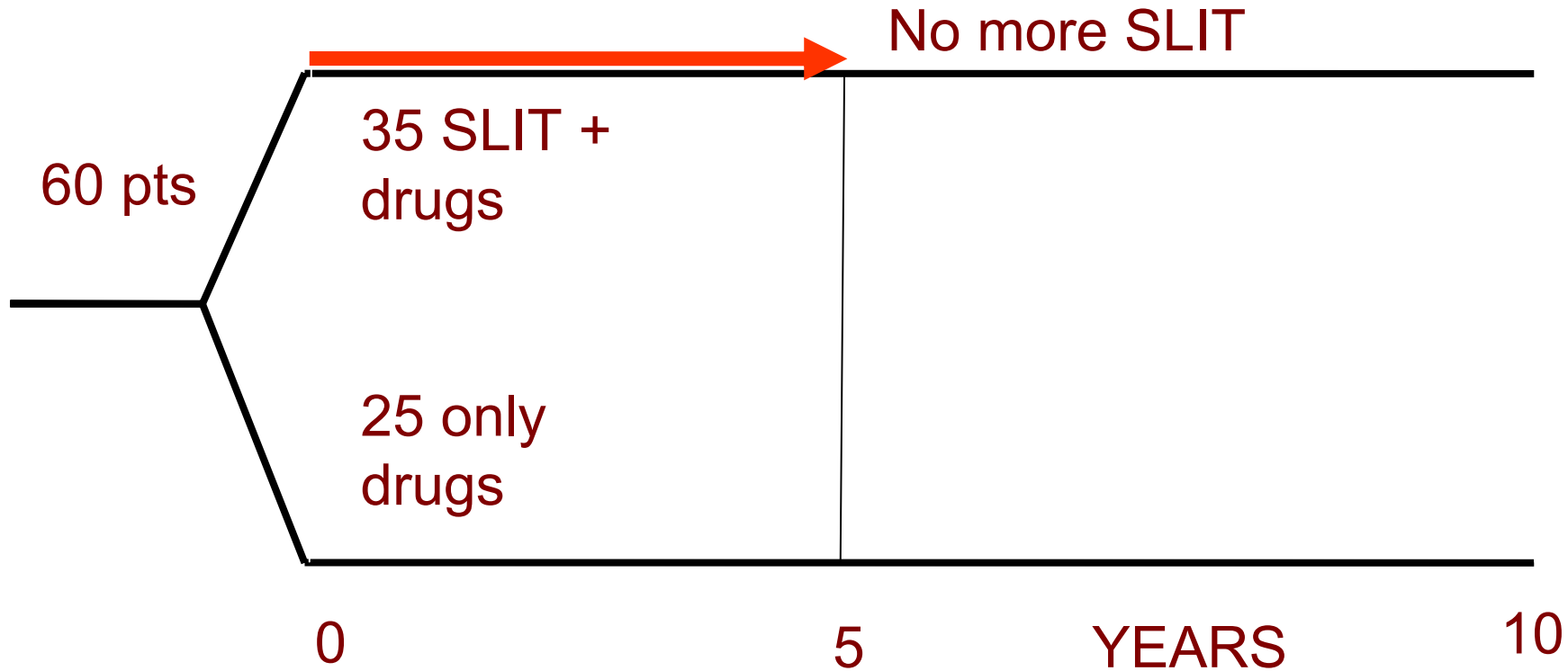
Evaluated at baseline, at term of treatment and after 4-5 years

Duration of evaluation: 10 years

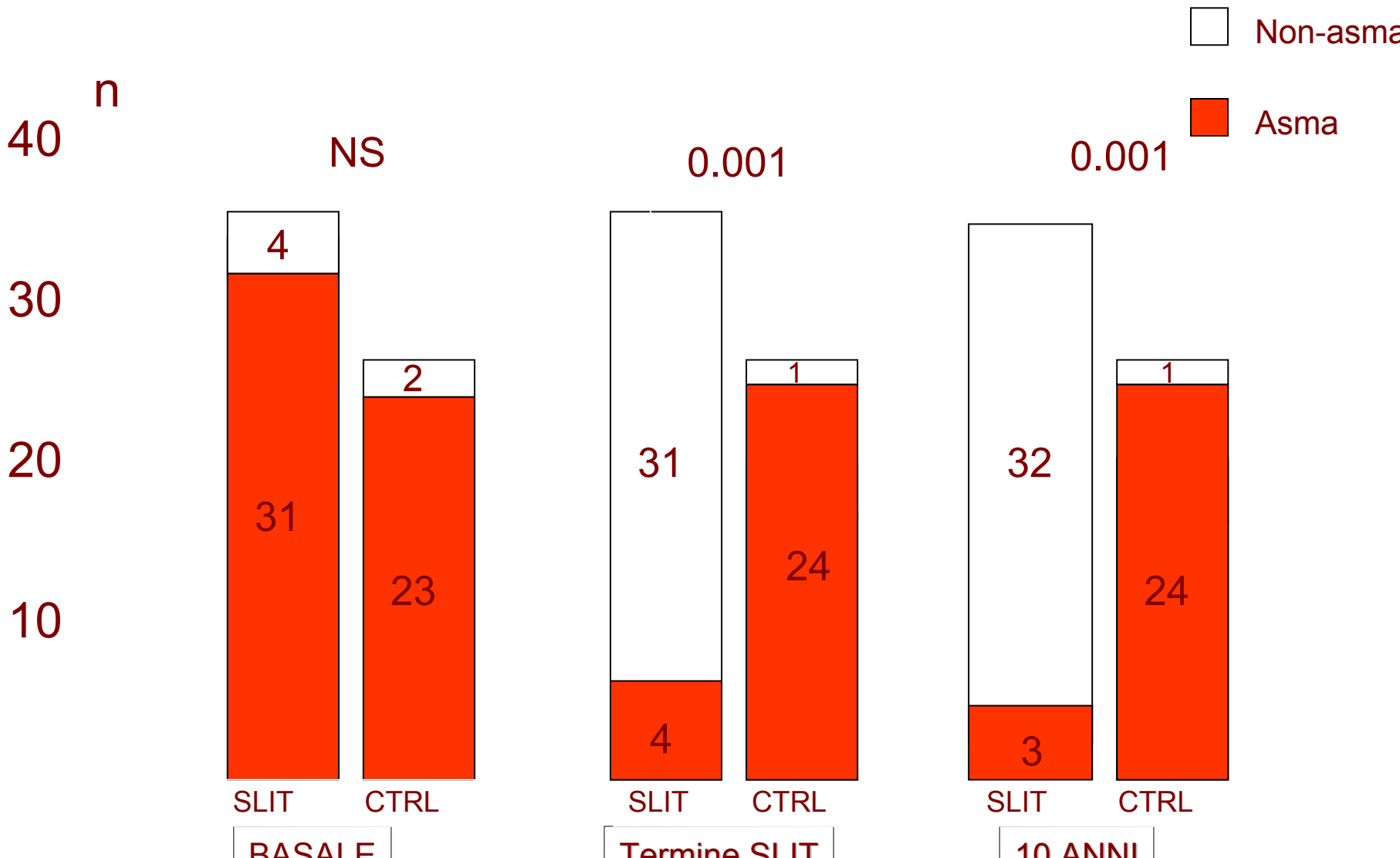
No significant side-effects reported



Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a ten-year prospective study



Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite



Indicazioni all'immunoterapia specifica nell'asma

L'ITS può essere indicata nei pazienti con asma allergico, da lieve a moderato, specialmente quando l'asma è associato a rinite, in accordo con le indicazioni già definite.

Lo scopo è quello di ridurre i sintomi ed il consumo di farmaci, nonché di **interferire con la storia naturale della malattia.**

L'immunoterapia ed il trattamento farmacologico non sono mutuamente esclusivi.

L'immunoterapia non deve essere somministrata a pazienti con asma severo persistente o non adeguatamente controllato dalla terapia.

Allergen Immunotherapy: A Practice Parameter Update

Statement: IT for children is effective and often well tolerated,...should be considered, (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, **allergic asthma... . prevent the new onset of new sensitization (A)**

Allergen Immunotherapy: A Practice Parameter Update

Statement: In recent studies, IT demonstrated

- decreased risk of development of asthma in children with allergic rhinitis;
- decrease in development of new sensitivities;
- modification in release of mediators in children on immunotherapy that correlates with decrease in clinical symptoms.

Allergen Immunotherapy: A Practice Parameter Update

Since allergen-SIT is a disease modifying treatment, **it should be initiated early** in the course of the disease in order to prevent irreversible damage in mucous membranes of the shock organ.

Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore, the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. (A)

Allergen Immunotherapy: A Practice Parameter Update

Statement 69 Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore, the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. (A)



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IT in younger children: current recommendations

WHO Position Paper. Allergen immunotherapy:
therapeutical vaccines for allergic diseases.

- The use of allergen immunotherapy in children requires a consultation with a specialist
- Most specialists prescribe immunotherapy after the age of 5 years.
- Controlled studies on the benefits versus risks of immunotherapy in patients below 5 years of age are needed





IT in younger children: current recommendations

EAACI. Immunotherapy: position paper.

- Immunotherapy should be started early in the disease process, meaning rather early in the lives of most patients.
- It is desirable to evaluate more closely in controlled studies the benefits of IT in patients < 5 years of age
- In a study [...] systemic reactions were recorded more frequently in children below 5 years of age
- Immunotherapy in young children (below 5 years of age) should be performed only by specialists with full capability of treating anaphylactic reactions in that particular age group



IT in younger children: current recommendations

Allergic rhinitis and its impact on asthma

- SLIT should be initiated early in the disease process
- Minimum age for onset of treatment not indicated





IT in younger children: current recommendations

Allergen immunotherapy. A practice parameter

- Some studies found IT effective < 5 years of age
- In rhinoconjunctivitis, IT may prevent asthma
- Usually not necessary < 5 years because pollen sensitivities develop later in childhood
- Systemic reaction difficult to recognize
- Injections can be traumatic to very young children





IT in younger children: current recommendations

Allergen immunotherapy. A practice parameter

- Children <5 years of age may have difficulty cooperating with an immunotherapy program
- The physician should carefully consider the benefits and risks of immunotherapy and individualize treatment in patients younger than 5 years of age.





Side-effects of SLIT: a review

619 patients (472 adults , 218 children),

Rhinoconjunctivitis and/or mild-to-moderate asthma

Duration of treatment: 4 months-2 years

347 (grass, ragweed, parietaria, olive, HDM) → 145 ae (41.7%)

343 placebo → 79 ae. (23.0%)

No difference in the frequency of AE between adults and children





Side-effects of SLIT: a methanalysis

Adverse events	Children		Adults		Whole population	
	Placebo	Treated	Placebo	Treated	Placebo	Treated
Cutaneous reactions	2	4	10	10	12	14
Oral itching-lip oedema	11	27	13	50	24	77
Rhinitis	9	10	6	14	15	24
Gastrointestinal	6	24	10	29	16	53
Mild asthma	6	12	18	9	24	21
Conjunctivitis	1	9	4	2	5	11
Laryngeal oedema	0	1	0	1	0	2
Aphthous ulcers	1	0	0	1	1	1
Weakness	0	1	0	0	0	1
Other	0	1	16	9	16	10
Totale	36	89	77	125	113	214
Totale %					23%	44%

p<0.001 p<0.05 p<0.02 p<0.001

Passalacqua G. Oral and sublingual

immunotherapy in paediatric patients. Curr Opin Allergy Clin Immunol. 2003;3:130-45



Safety of sublingual immunotherapy with a monomeric allergoid in very young children.

A safety survey

36 children (age 23 – 46 months, mean 38 months)

Allergic to mites – 19

Allergic to grass – 17

SLIT aqueous (monomeric allergoid, LAIS – Lofarma)

Mean follow-up 22.2 months





Safety of sublingual immunotherapy with a monomeric allergoid in very young children.

36 children (age 23 – 46 months, mean 38 months)

Persistent asthma – 17

Intermittent asthma – 12

Rhinoconjunctivitis – 33

2 side effects (abdominal pain) : 25,200 doses

< 0.01 side effects/100 doses



Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

Alessandro Fiocchi	Melloni Paediatria, Milan
Giovanbattista Pajno	University School of Medicine, Messina,
Stefania La Grutta	Allergy Unit, Children Hospital, ARNAS, Palermo
Francesco Pezzuto	Allergy Unit, ASL SA2, Salerno
Cristoforo Incorvaia	Allergy/Rheumatology Unit, ICP Hospital, Milan
Francesco Marcucci	University School of Medicine, Perugia
Lausa Sensi	University School of Medicine, Perugia
Franco Frati	University School of Medicine, Perugia



Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

Objectives

- A pilot study
- Research question: is the 5-year cut-off point relevant in terms of safety for children aged 3 to 7 years?





Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

Design

- Observational, multi-center study
- SLIT-sw prescribed for rhinoconjunctivitis and/or asthma in children under seven years of age
- Monosensitisation towards pollen or mite allergen
- Rhinoconjunctivitis, allergic asthma or both
- GINA < II
- ARIA intermittent severe or persistent
- Primary outcome: onset of adverse reaction irrespective of triggering dose or phase of treatment





Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

SLIT schedule

- Staloral 300[®] (Stallergènes, Antony, France)
- Build-up phase in 11 days
- Maintenance phase - 300 IR three times a week





Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

Population

- 65 children [14F, 51M]
- 38-80 months (m 60 ± 10.15)
- Group A: 38-60 months (33 children; m 52 ± 6.00)
- Group B: 61-80 months (32 children; m 70 ± 10.6)
- Mean duration of treatment 246 ± 161 days
- HDM (n=42), grass (n=11), olive tree (n=5), *Parietaria* (n=4) and cypress pollens (n=3).





Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

	Group A	Group B
# reactions/patients	6/5	7/6
# reactions/doses	1:608	1:502
χ^2 (A vs. B)	0.0348	$P = ns$
P adverse outcome per patient	0.16 ± 2.34	0.17 ± 2.20





Importance of allergy diagnosis in young children

When the allergic march starts, diagnosis should be made

Host A. Allergy testing in children: why, who, when and how? *Allergy* 2003; 58:559-6

Fiocchi A. Differential diagnosis of IgE-mediated allergy in young children

Ann Allergy Asthma Immunol 2004;93:328-3

Preventive effect of specific immunotherapy on the natural history of allergic disease

Moller C. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109:251-





Safety of sublingual/swallow immunotherapy in children aged 3 to 7 years.

- There is no reason to forbear assessing safety and efficacy at age younger than five years.
- Well-controlled clinical studies will establish the safety of SLIT-sw among toddlers.
- IT vs natural history?
- Single allergens?
- Doses?.....





Standards for practical allergen-specific immunotherapy: sublingual immunotherapy - paediatric aspects

- The excellent safety profile of sublingual immunotherapy
- The fact that injections are not required with this method raise the possibility that sublingual immunotherapy could be given to children below the age of 5 years
- Try to modify the natural course of the allergic disease
- At present this is speculation
- Definitive trials are required



E. Alvarez-Cuesta, J. Bousquet, G. W. Canonica, S. R. Durham, H.-J. Malling, E. Valovirta. EAAACI immunotherapy task force. Standards for practical allergen-specific immunotherapy *Allergy* 2006



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Società Italiana per le Malattie
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