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Wheezing, concomitanze, complicanze ed asma

Alessandro Fiocchi,
Caserta,
18 aprile 2013

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Wheezing, asma o....?

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Adrian, clinical history (highlights)

- Day-care center since age 6 months
- Now, 10-months old: “always coughing”
- Only sporadic febrile episodes, at most 38°5 rectal
- Treated with

a. An antibiotic course (amoxycillin, 50mg/kg/day for 8 days)
b. Aerosol bronchodilators
c. Mucolytics

- Once diagnosed with “asthmatic bronchitis”
- Twice diagnosed with “bronchospasm”
- Once diagnosed with asthma attack, oral steroids administered

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Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach

Definitions of phenotypes

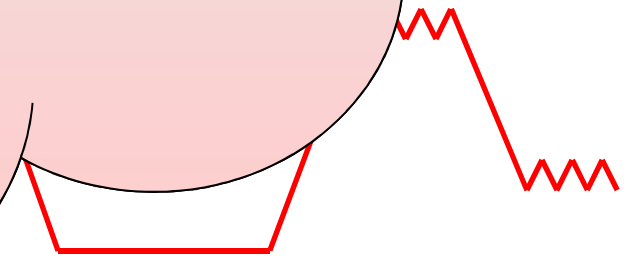
For clinical purposes, wheeze should be described in terms of its temporal pattern and classified as episodic (viral) or multiple-trigger wheeze.

The term asthma should probably not be used in preschool children because data regarding underlying inflammation are lacking.

Epi

Mu

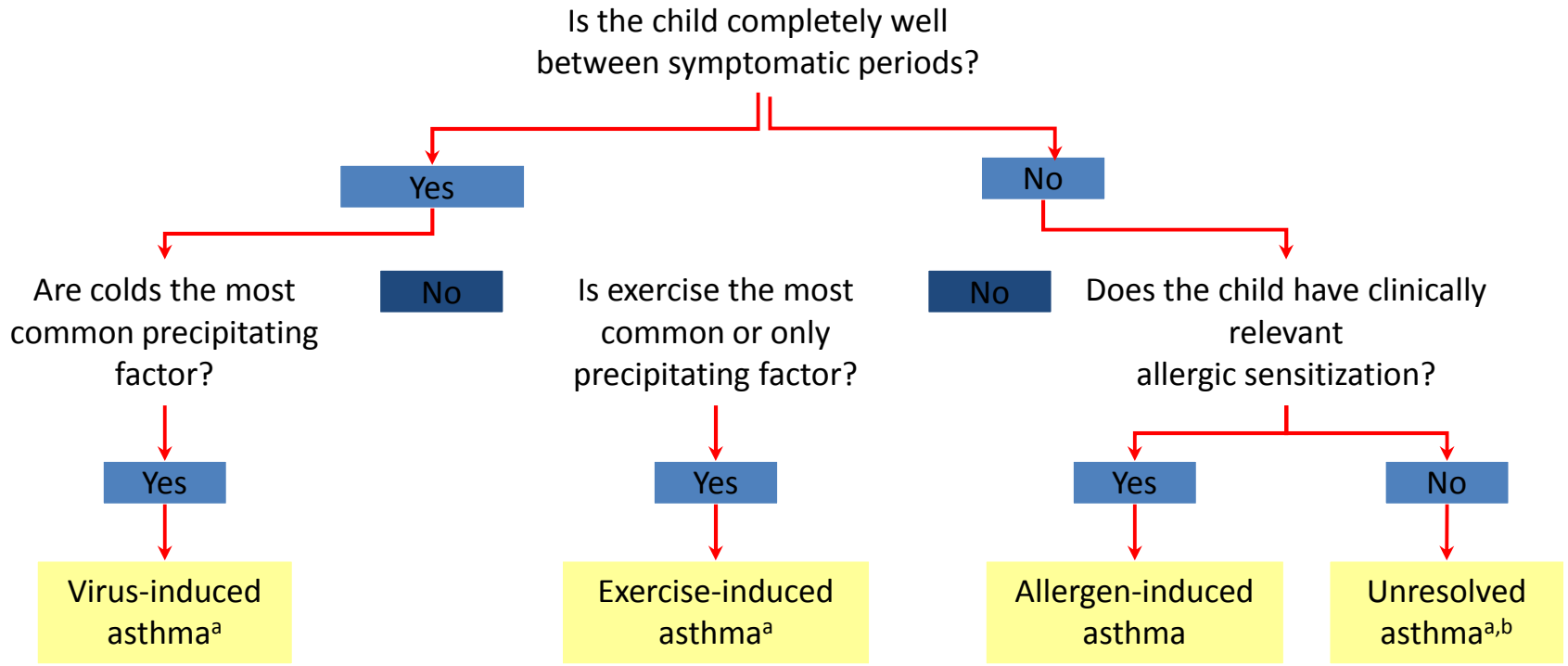
wheez



Brand PL. Definition, assessment an heezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008; 32:1096-110.

Identification of Asthma Phenotypes is Critical

Asthma Phenotypes in Children



[a]Children may also be atopic.

[b]Different etiologies, including irritant exposure and as-yet not evident allergies, may be included here.

Adapted from Bacharier LB, et al. Allergy. 2008;63(1):5–34.

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Phenotypes according to trigger

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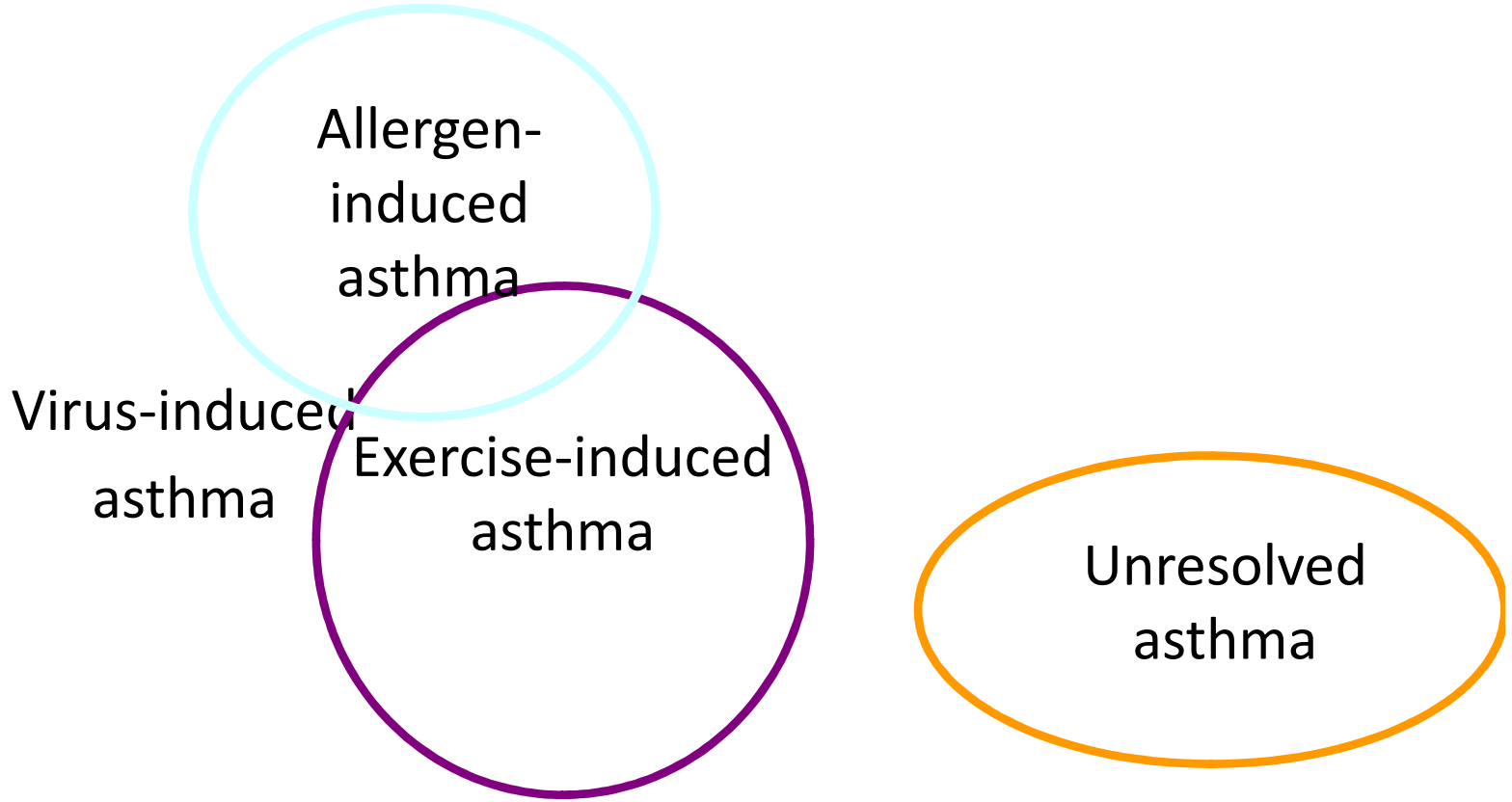
Asthma Phenotypes in Children



Virus-induced asthma[a]

Exercise-induced asthma[a]

Allergen-induced asthma

Unresolved asthma[a,b]

Bacharier LB, et al. *Allergy.* 2008;63(1):5–34.

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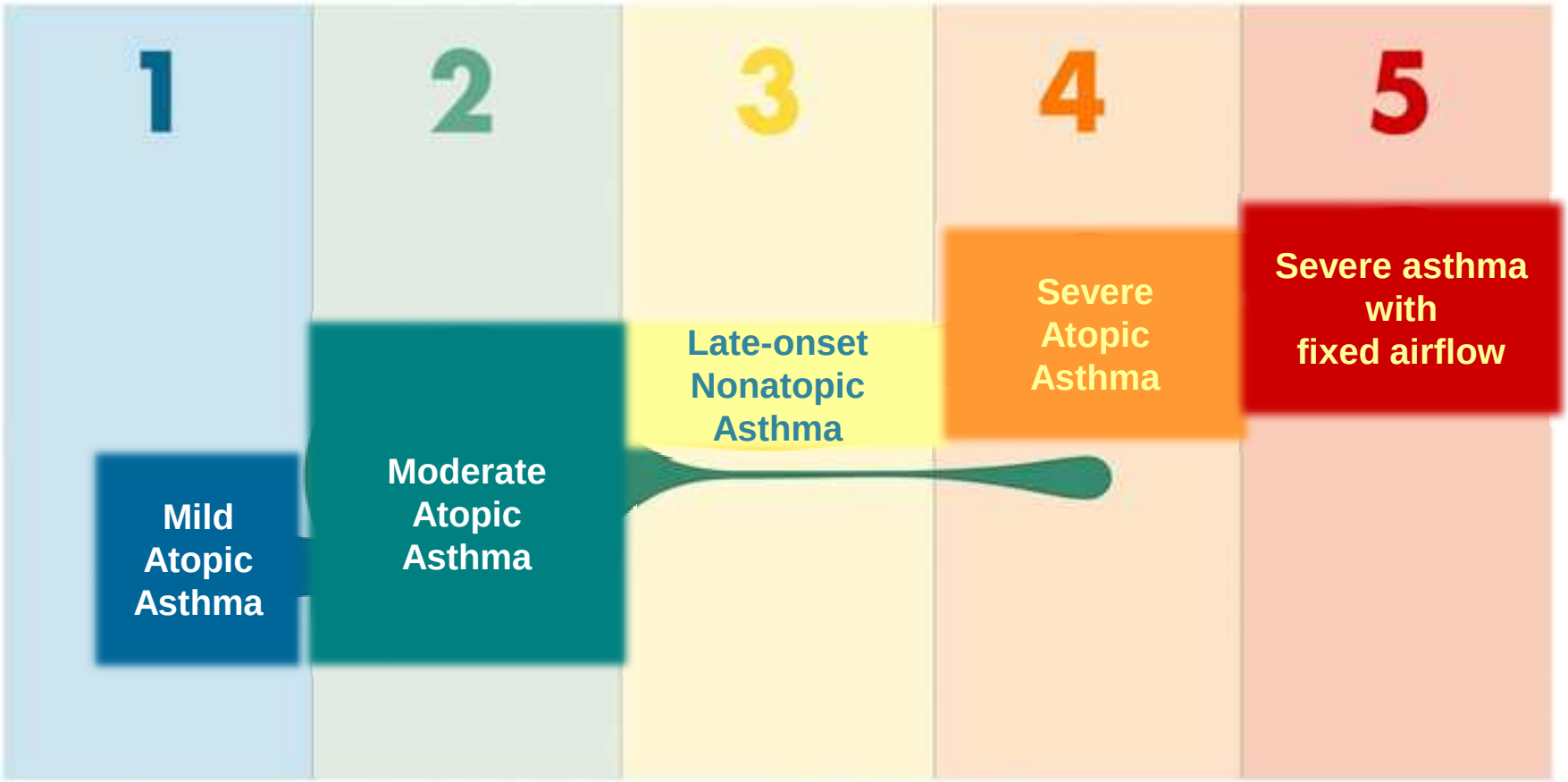
SARP Phenotypes: cluster analysis



Moore WC. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181:315-23

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Asthma in Childhood: Recent Advances in Phenotyping and Pathogenesis

Subgroups with differences in lung function, age of asthma onset, inflammatory features and clinical treatment responses

In children → four unique cluster phenotypes of asthma defined by different degrees of lung function, asthma duration, and asthma controller medication use

No cluster corresponded to the asthma severity classifications proposed in asthma treatment guidelines

Fitzpatrick AM. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart,Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011; 27:382–9.

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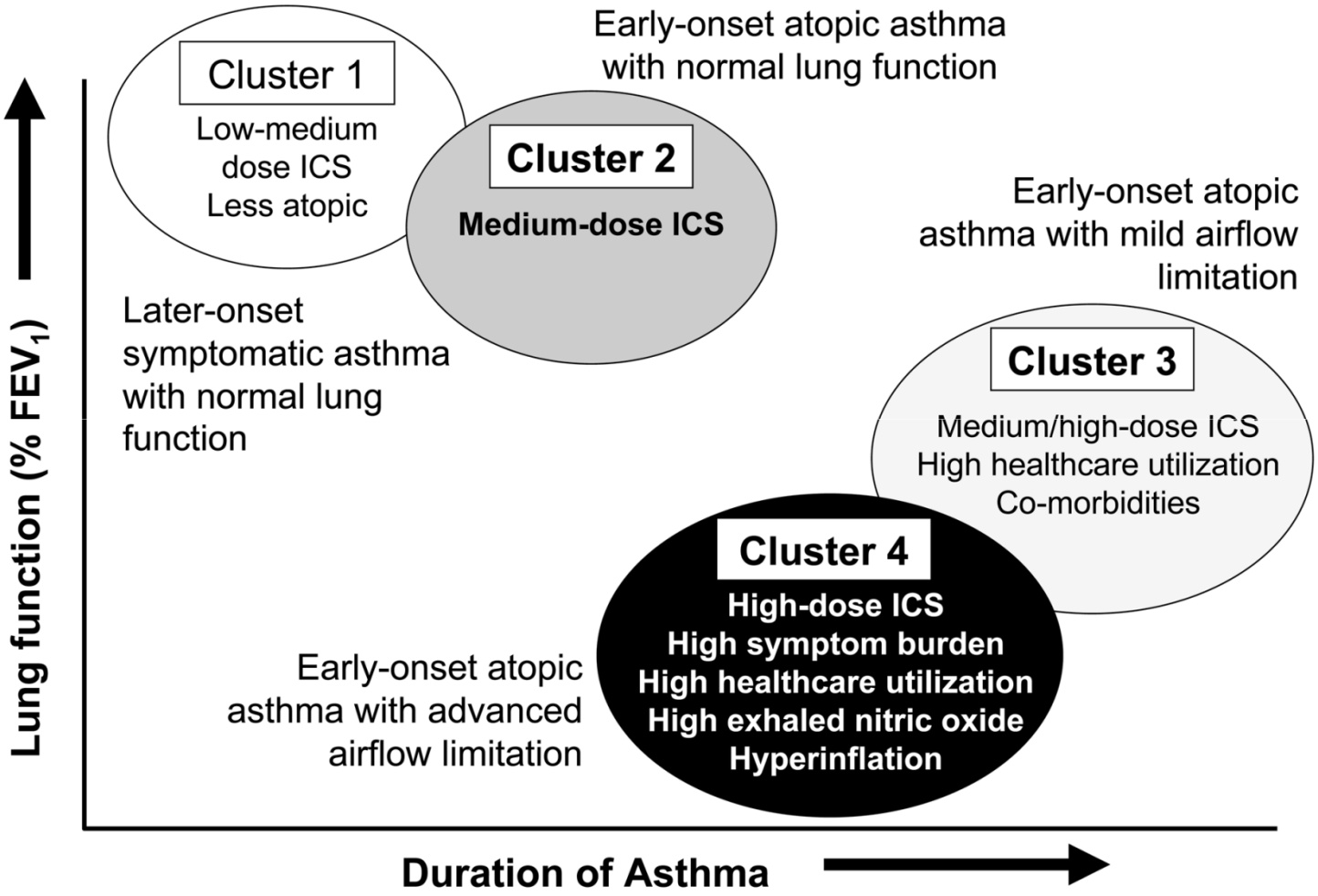
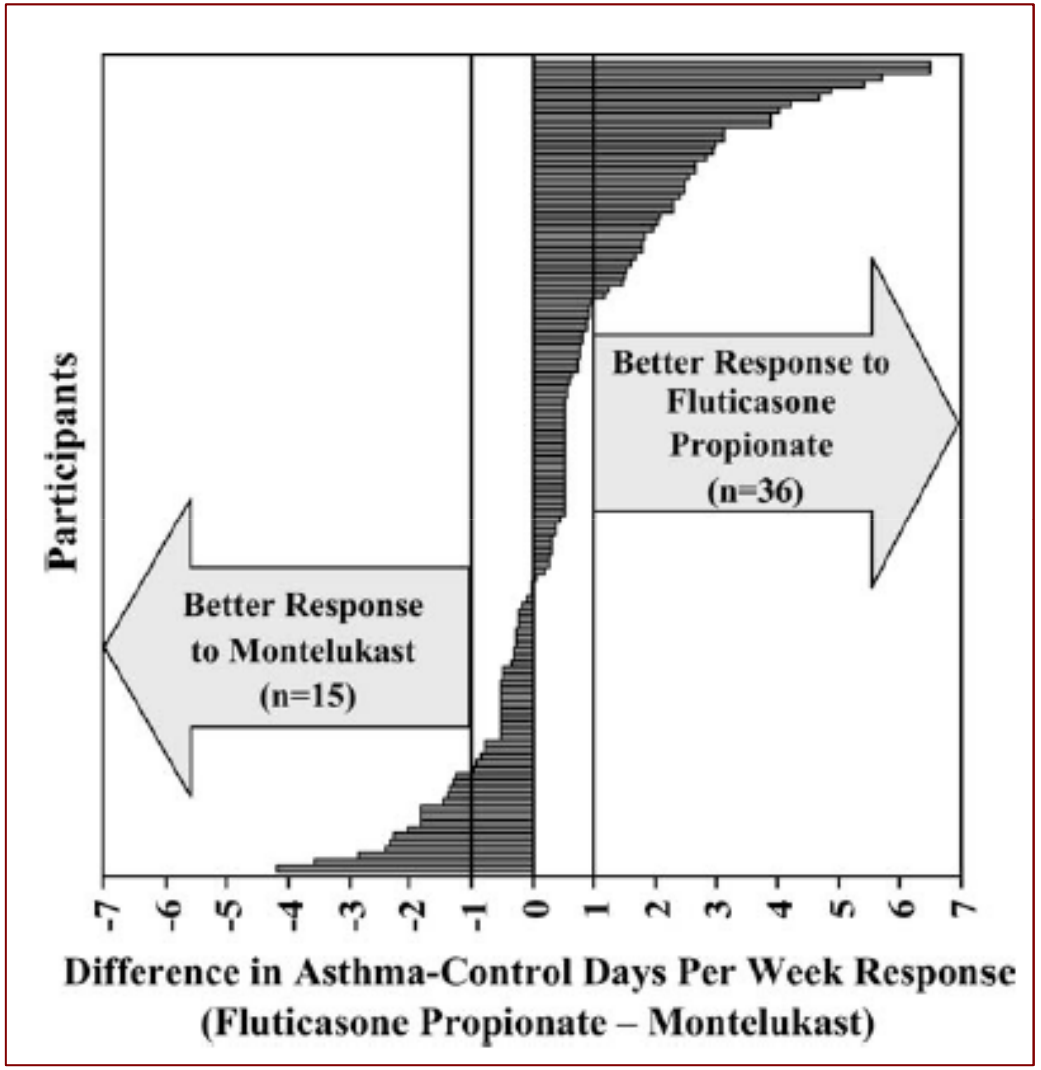
Clusters of asthma by phenotypic features



Fitzpatrick AM. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart,Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011; 27:382–9.

Different response profiles



Zeiger RS. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006;117:45-52

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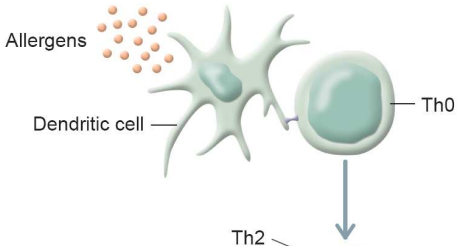
Wheezing, asma o....?

La rinite allergica è fattore di sviluppo per l'asma



Fiocchi A, Fox AT. Preventing progression of allergic rhinitis. Arch Dis Child 2011;96:91-100

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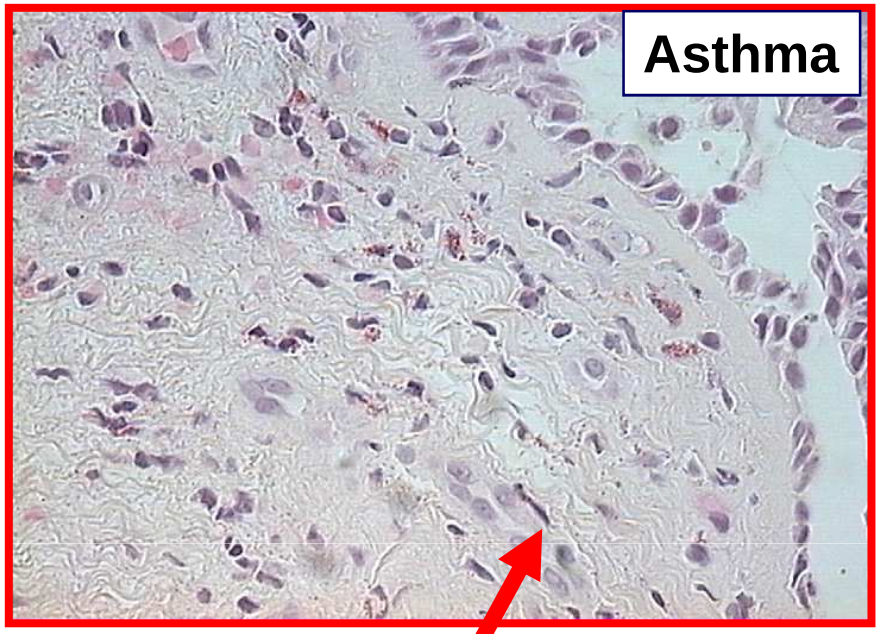
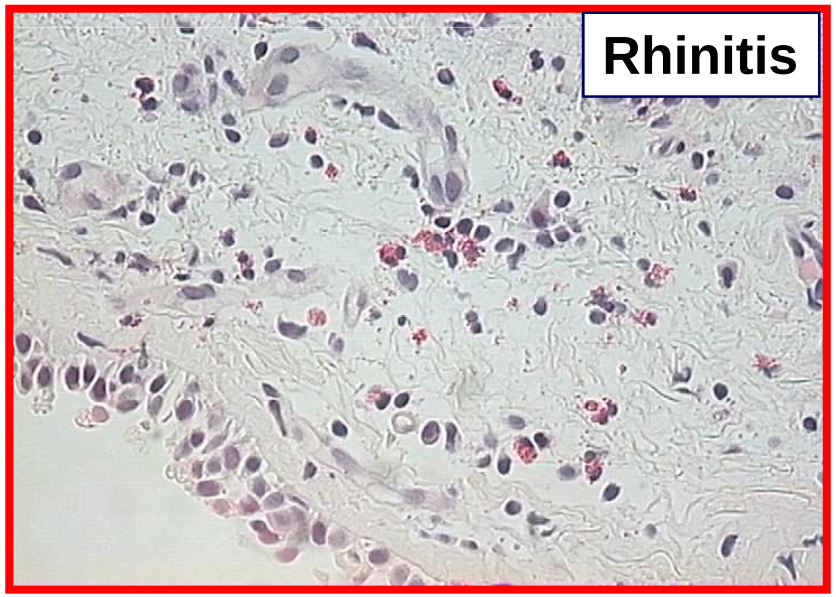


Bronchial biopsies in allergicic patients
with asthma or rhinitis
after specific challenge



Bronchial inflammation is identical

Crimi E. Inflammatory and mechanical factors of allergen-induced bronchoconstriction in mild asthma and rhinitis. J Appl Physiol. 2001;91:1029-34

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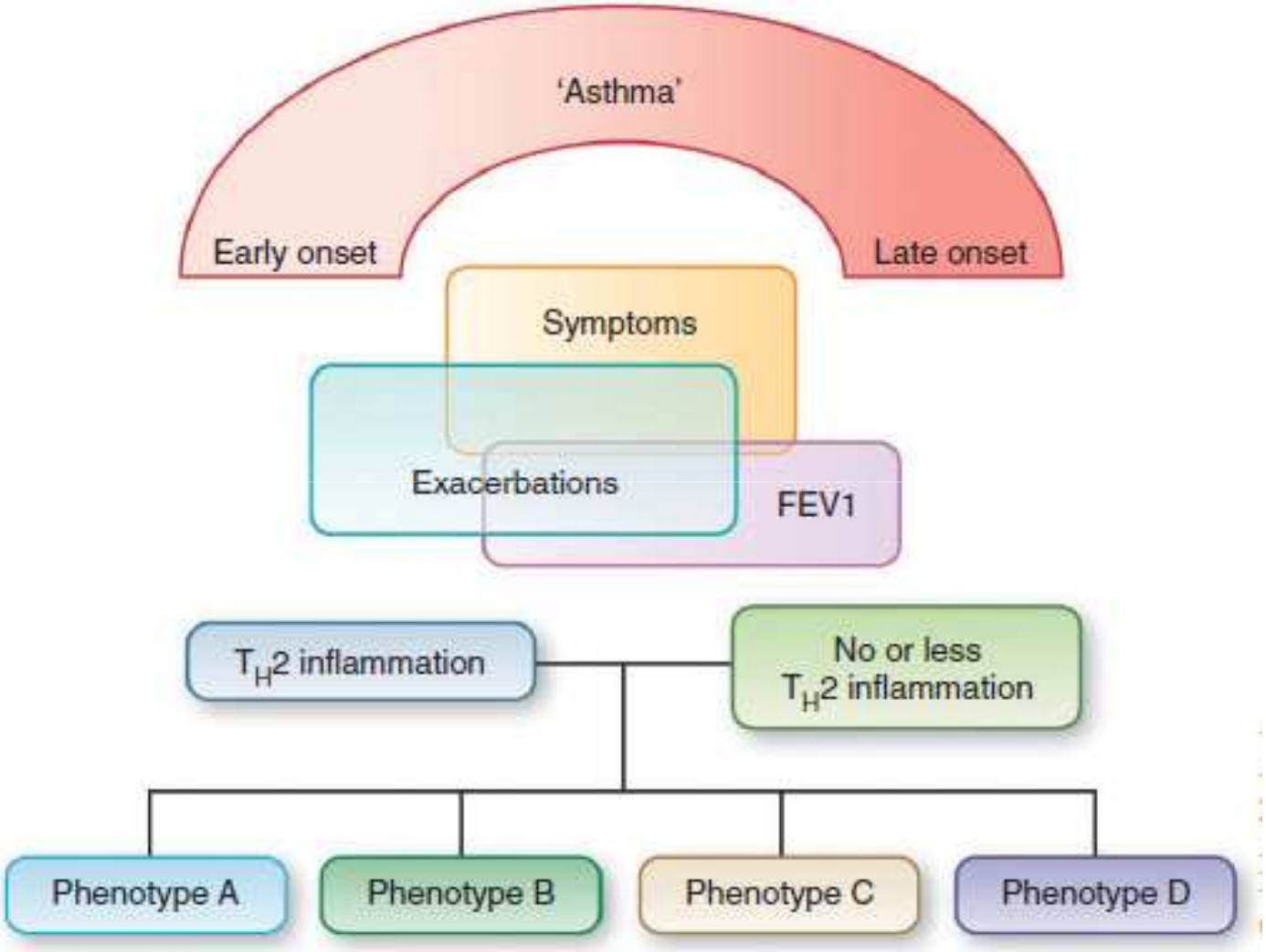

Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature Medicine 2012; 18:716-25


Coca-Cola
cherry
Coca-Cola
lemon
Coca-Cola
lime
Coca-Cola
vanilla

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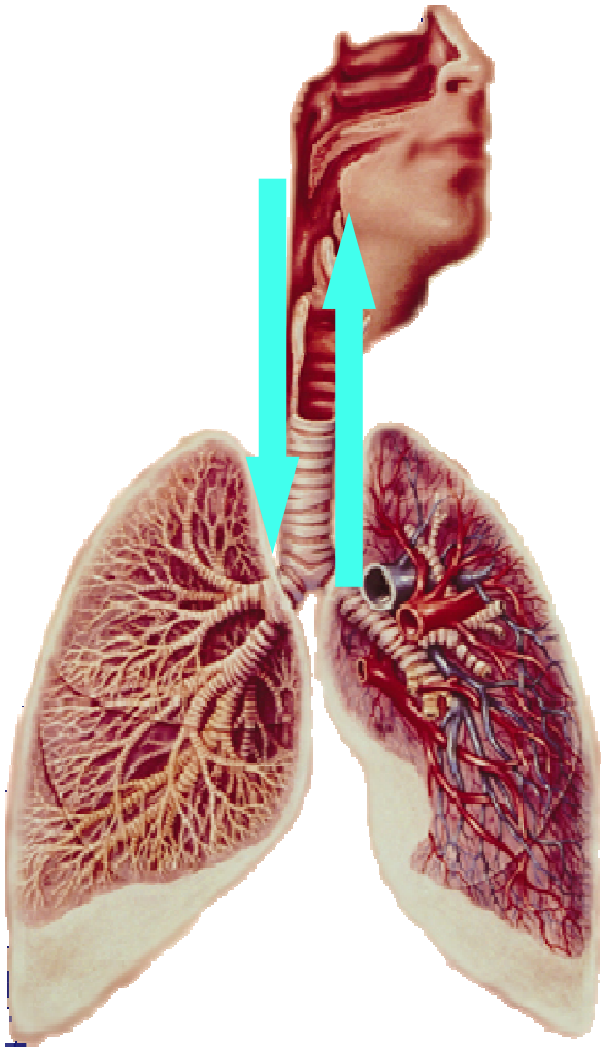

“United Airways Disease“

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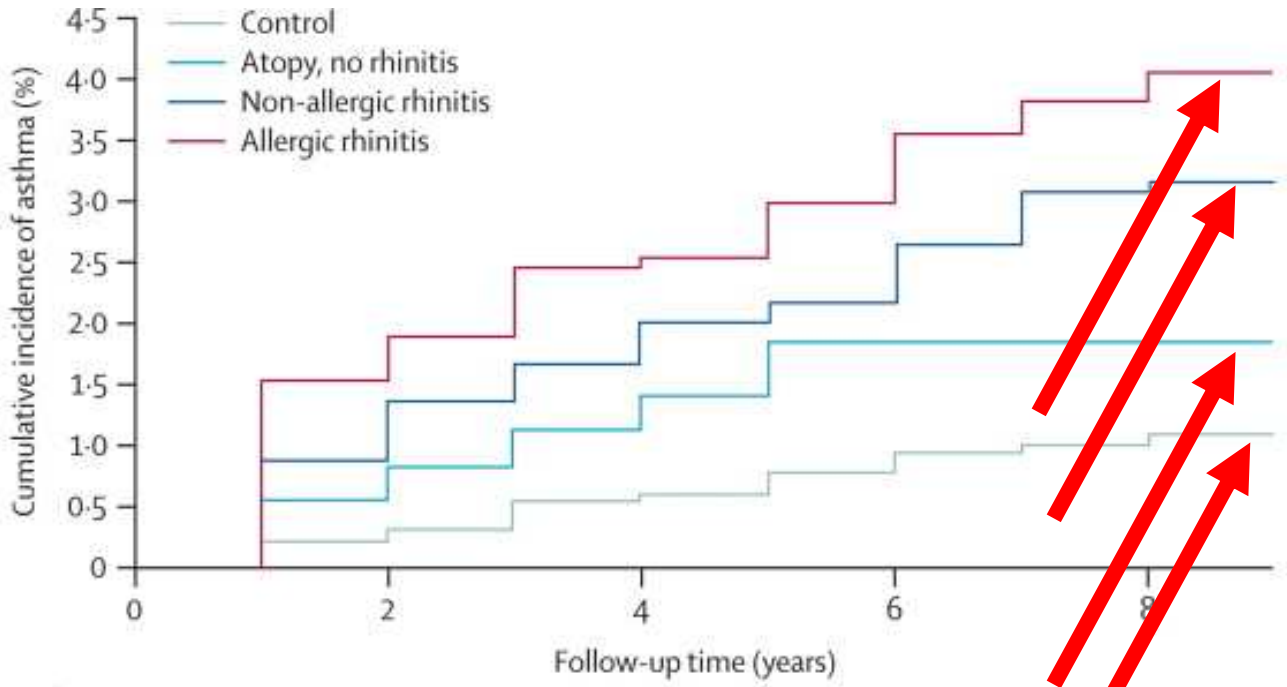
Risk factors for asthma

Wheezing Phenotype	% in each category at age 6 years	Significant risk factors for each phenotype
Never Wheezed	51.5%	Reference Group
Transient Early Wheezers	19.9%	Maternal smoke exposure
Late-onset Wheezers	15%	**Rhinitis apart from URIs** Maternal asthma Male sex
Persistent Wheezers	13.7%	Eczema **Rhinitis apart from URIs** Maternal asthma Male sex Maternal smoke exposure

Martinez FD. New insights into the natural history of asthma: primary prevention on the horizon. J Allergy Clin Immunol. 2011;128:939-45

La rinite allergica è fattore di rischio per lo sviluppo di asma



Number at risk

Control	3163	3158	3153	3064	2967
Atopy, no rhinitis	704	701	698	669	642
Non-allergic rhinitis	1377	1396	1358	1268	1199
Allergic rhinitis	1217	1208	1194	1093	1038

Probability of developing asthma, % (95% CI)

Control	0	0·2 (0·1–0·5)	0·5 (0·3–0·9)	0·8 (0·5–1·2)	1·0 (0·7–1·5)
Atopy, no rhinitis	0	0·6 (0·2–1·5)	1·1 (0·6–2·3)	1·9 (1·1–3·2)	1·9 (1·1–3·2)
Non-allergic rhinitis	0	0·9 (0·5–1·5)	1·7 (1·1–2·5)	2·2 (1·5–3·1)	3·1 (2·3–4·1)
Allergic rhinitis	0	1·6 (1·0–2·4)	2·5 (1·7–3·5)	3·0 (2·2–4·1)	3·8 (2·9–5·1)

Shaaban R. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008; 372(9643):1049-57

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Cross-sectional studies examining the relationship between rhinitis and asthma in pediatrics

Author	Population	Findings
Peroni D	N 1,402 ages 3–5 years	Rhinitis: ⇧ asthma (20.8 vs 6.2%, P .0001)
Bugiani	17,666 ages 20–44 years	Allergic rhinitis associated with asthma (OR, 7.89; 95% CI, 7.07–8.08).
Leynaert	N 10,210; ages 20–44 years	Rhinitis: ⇧ asthma (OR, 6.63; 95% CI, 5.44–8.08) ⇧ BHR (OR, 3.02; 95% CI, 2.66–3.43)

Peroni DG. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. Clin Exp Allergy. 2003;33:1349–54.
Leynaert B. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol. 2004;113:86 –93
Bolgiani M. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy. 2005;60:165–170.

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Rhinitis in infancy is a risk factor for asthma in adulthood

- a 20-year follow-up
- a threefold increased risk of developing asthma
- rhinitis was diagnosed before asthma in 76% of the patients
- rhinitis is a significant independent risk factor for asthma

Guerra S. Rhinitis as an independent risk factor for adult-onset asthma.
J Allergy Clin Immunol 2002; 109:419–425

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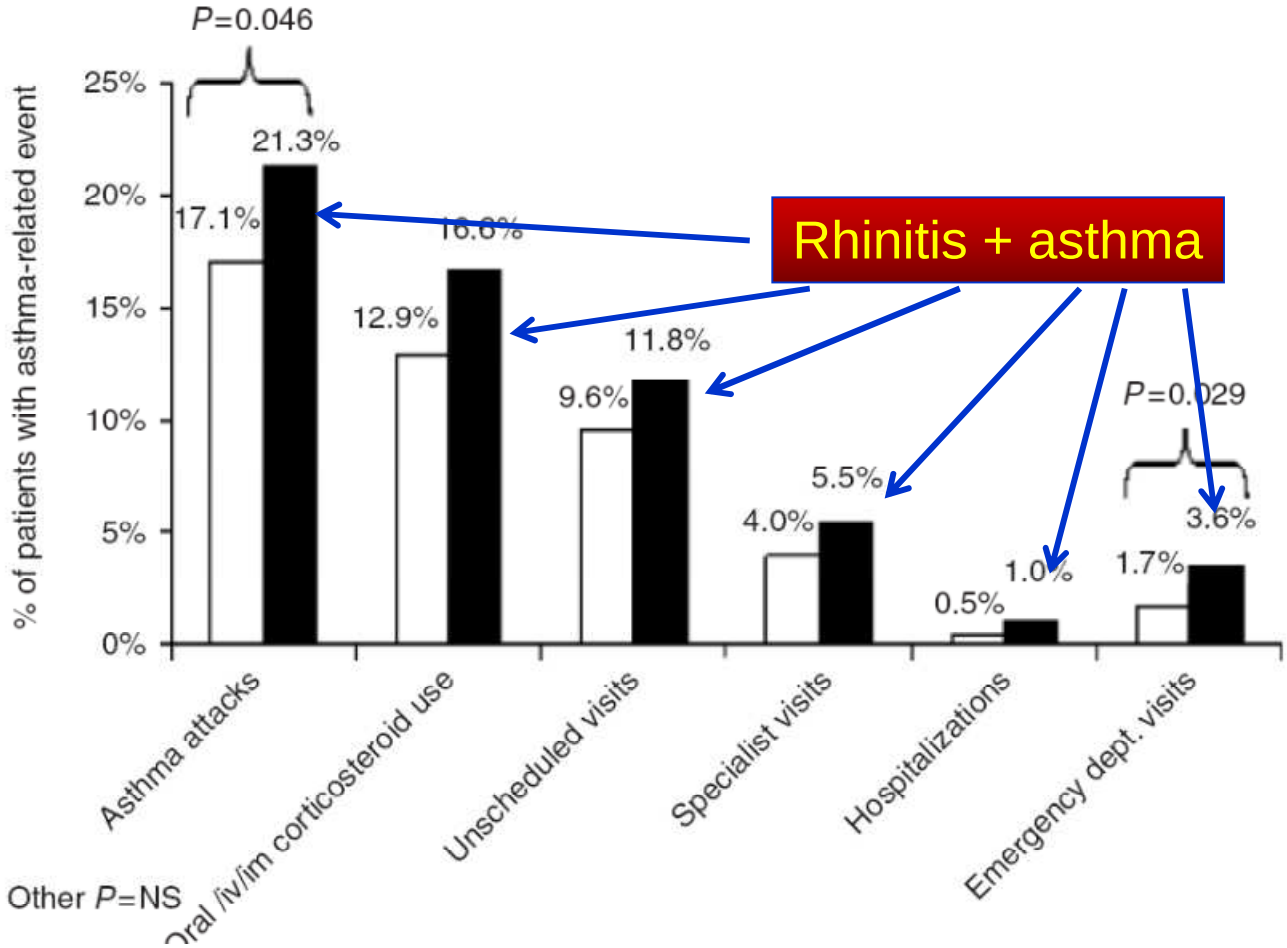
Allergic rhinitis is associated with asthma severity



Bousquet J. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis. Clin Exp Allergy 2005; 35:723–727

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The relationship between rhinitis and asthma

- Asthma in patients with rhinitis: 10 - 40%
- Rhinitis among asthmatic patients: up to 80%
- Rhinitis is powerful predictor of adult-onset asthma
- Rhinitis + atopy is an even stronger predictor of adult-onset asthma
- Rhinitis is associated with severe asthma, at risk for attacks

Ker J. The atopic march: what's the evidence?
Ann Allergy Asthma Immunol. 2009;103:282–9

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Recommendations of the ARIA workshop

1. Allergic rhinitis is a major chronic respiratory disease due to its:
- Prevalence
- impact on quality of life
- impact on work/school performance and productivity
- economic burden
- links with asthma

2. In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis

3. Allergic rhinitis should be considered as a risk factor for asthma along with other known risk factors

4. A new subdivision of allergic rhinitis has been proposed:
- Intermittent
- persistent

5. The severity of allergic rhinitis has been classified as mild or moderate/severe depending on the severity of symptoms and quality of life outcomes

Brozek JL. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision.
J Allergy Clin Immunol. 2010 ;126(3):466-76

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Recommendations of the ARIA workshop

6. Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed
7. The treatment of allergic rhinitis combines:
   - Allergen avoidance (when possible)
   - Pharmacotherapy
   - Immunotherapy
   - Education
8. **Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator**
9. Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis
10. A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety

Brozek JL. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision.
J Allergy Clin Immunol. 2010 ;126(3):466-76

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Il controllo clinico previene la marcia allergica

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Management of asthma in children 5 years and younger.

Asthma education should be provided to family members and caregivers of wheezy children 5 years and younger when wheeze is suspected to be caused by asthma.

For all patients with asthma, the goal of treatment is **to achieve control** of the clinical manifestations of the disease and maintain this control for prolonged periods, with appropriate regard to the safety and cost of the treatment required to achieve this goal.

Pedersen SE, Hurd SS, Lemanske RF Jr, Becker A, Zar HJ, Sly PD, Soto-Quiroz M, Wong G, Bateman ED. Global strategy for the diagnosis and management of asthma in children 5 years and younger. Pediatr Pulmonol. 2011; 46:1-17

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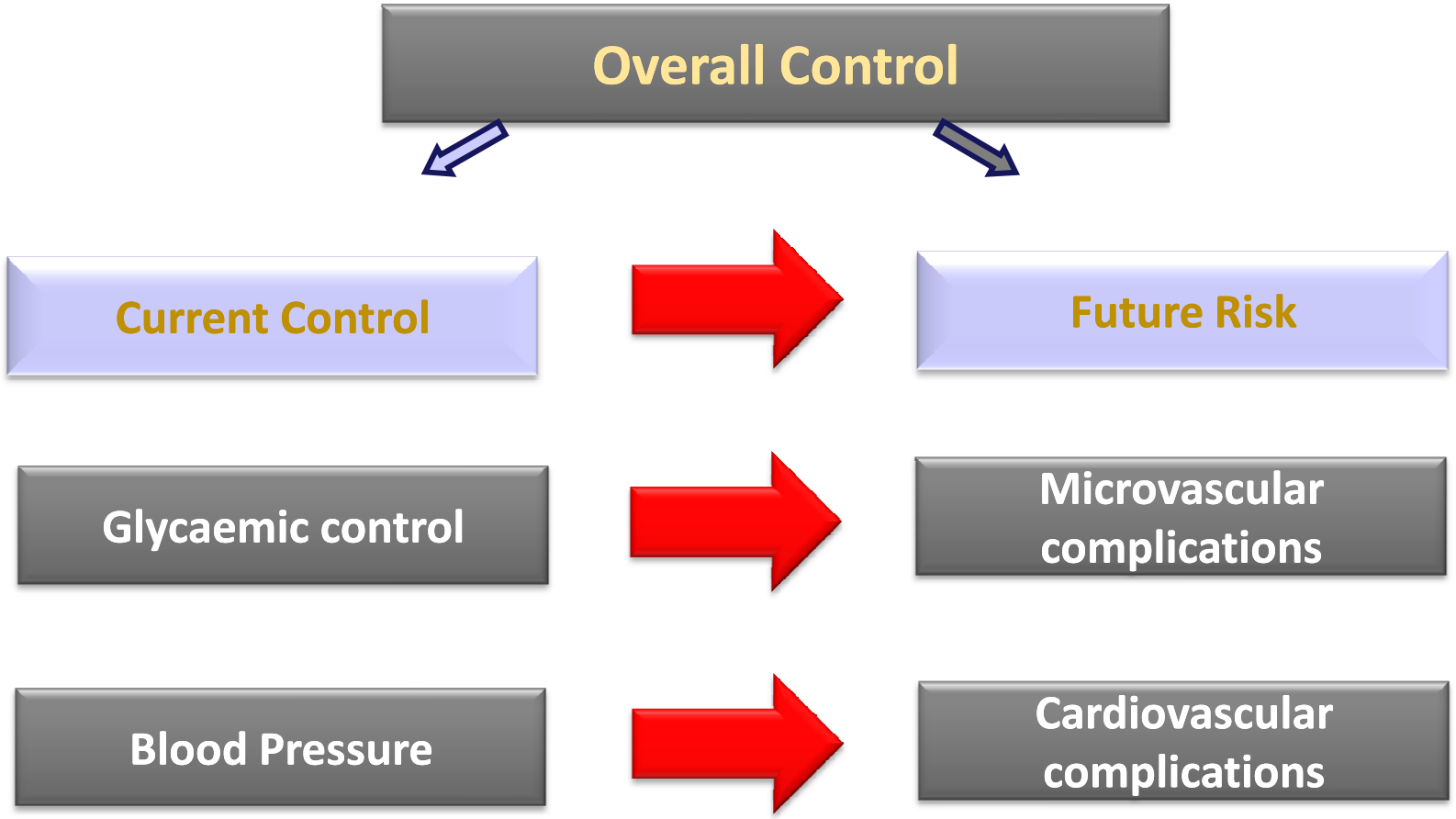
GINA: il controllo dell'asma

Nella settimana:	Controllato (tutti OK)	Controllo parziale (ce n'è uno)	Fuori controllo (tre o più)
Sintomi diurni. Fischio, tosse, difficoltà respiratoria	Nessuno (teh, ti permetto un paio di Ventolin la settimana…)	Più di un paio la settimana, ma vanno via col Ventolin.	Tanto Ventolin ed è difficile mandare via i sintomi
Limitazione delle attività	Nessuna – il bimbo gioca corre e fa casino	Fischia o tossisce se corre gioca o ride o piange	Fischia, tossisce e gli manca pure il fiato se corre gioca o ride o piange
Sintomi notturni - risvegli	Dorme e non tossisce	Dorme ma tossisce	Dorme ma tossisce e si puO' anche svegliare
Servono beta-2?	Non più di un paio di volte	Più di un paio di volte	Più di un paio di volte

LG Gina, 2009 – GINA Pediatric report, 2009 -

Measures of Clinical Control of Chronic Diseases



Bateman ED. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol 2010;125:600-8,

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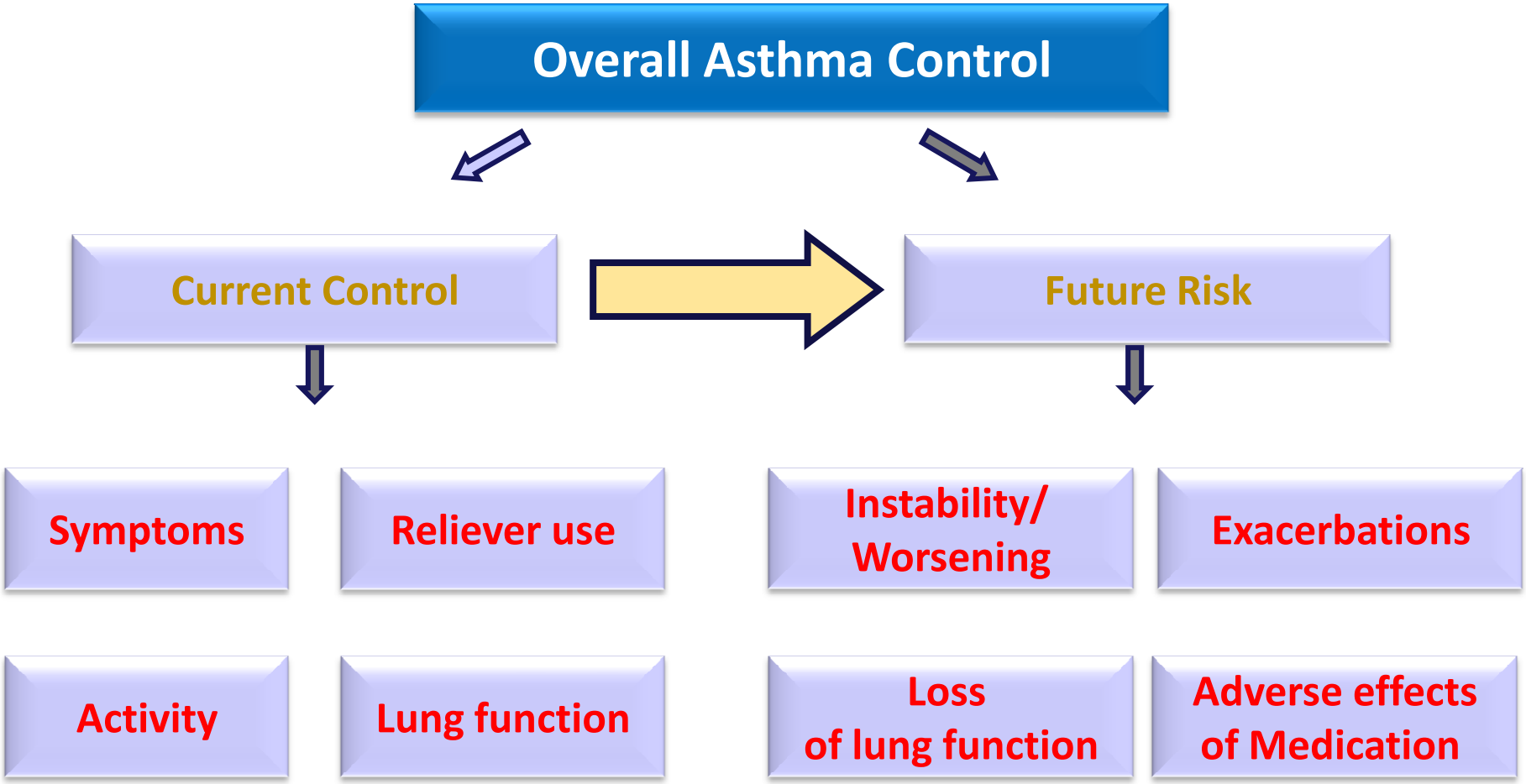
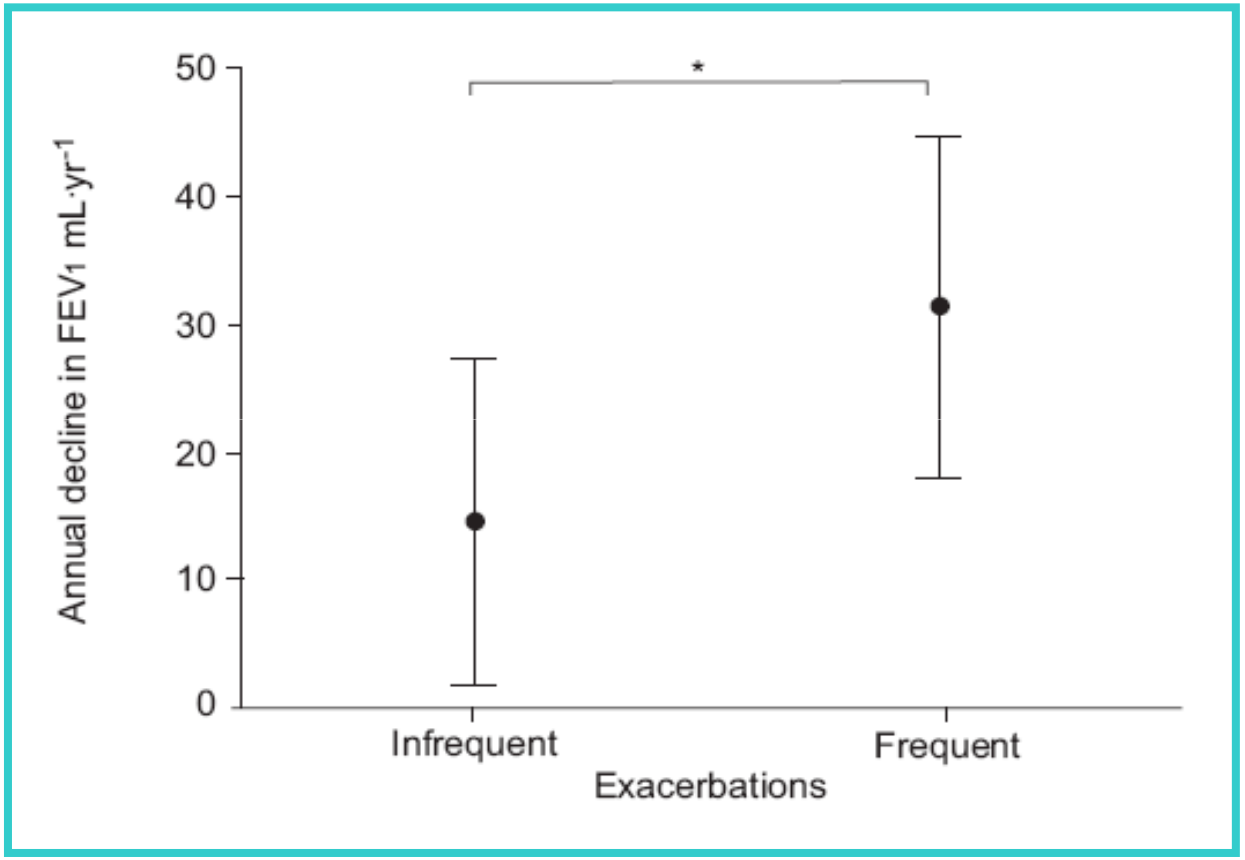
Goals of asthma management



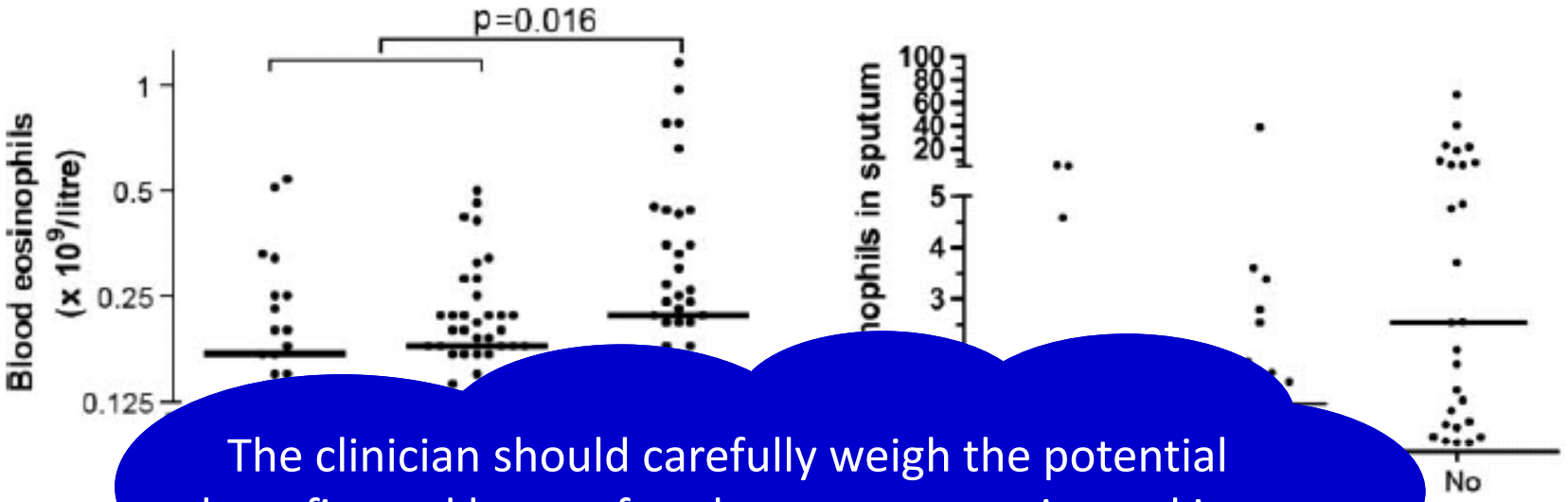
Bateman ED. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol 2010;125:600-8,

Severe exacerbations impact on FEV_1



Bai TR. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007;30:452-6

Relazione tra controllo clinico e flogosi bronchiale



The clinician should carefully weigh the potential benefits and harm of each treatment option, taking into account the unknown long-term (> one year) impact of intermittent therapy on lung growth and lung function decline.

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- esalato,

ipe pitelio integro)

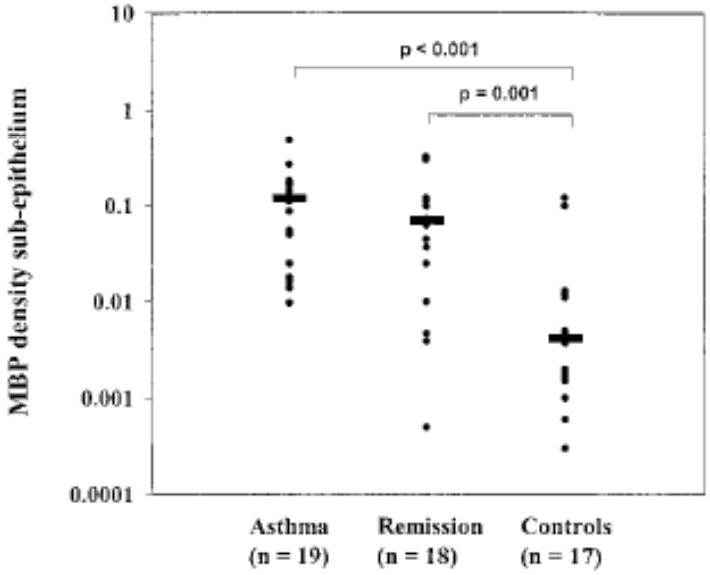
Prima dimostrazione di rela trollo clinico e riduzione dei marcatori diretti e indiretti di infiammazione bronchiale.

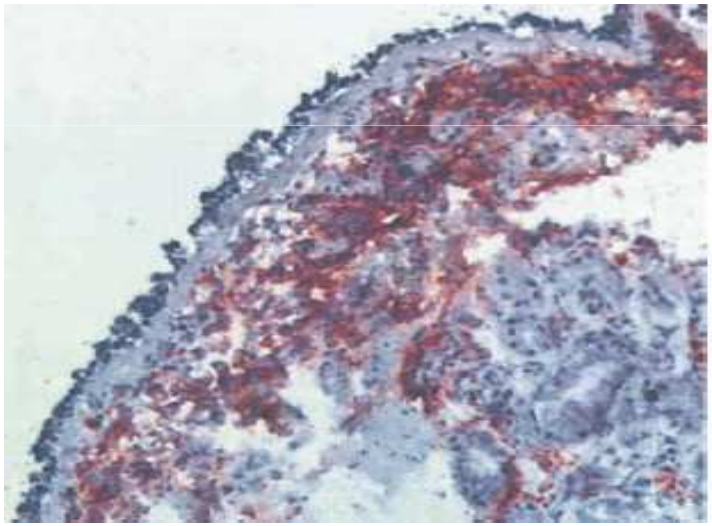
La terapia al bisogno non controlla la flogosi (*Boushey HA et al., NEJM 2005)*

Volbeda F. Clinical control of asthma associates with measures of airway inflammation. Thorax. 2013;68:19-24

Airway Inflammation Is Present during Clinical Remission of Atopic Asthma

Clinical remission: complete absence of asthmatic symptoms in subjects not taking any asthma medication for at least 12 mo prior to the study





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La rinite allergica è fattore di sviluppo per l'asma

Il controllo clinico previene la marcia allergica

Qual è la strategia terapeutica ottimale in pediatria?

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ETAC™ STUDY
Early Treatment of the Atopic Child

- Children aged 12 - 24 months, no asthma
- Family history of atopy
- Early AD
- Intervention: cetirizine 0.25 mg/kg two times per day *vs.* placebo for 18 months
- Outcome: time to onset of asthma.

ETAC™ Study Group. Pediatr Allergy Immunol 1998;9:116-124

Warner J. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' post-treatment follow-up. J Allergy Clin Immunol 2001;108:929–37

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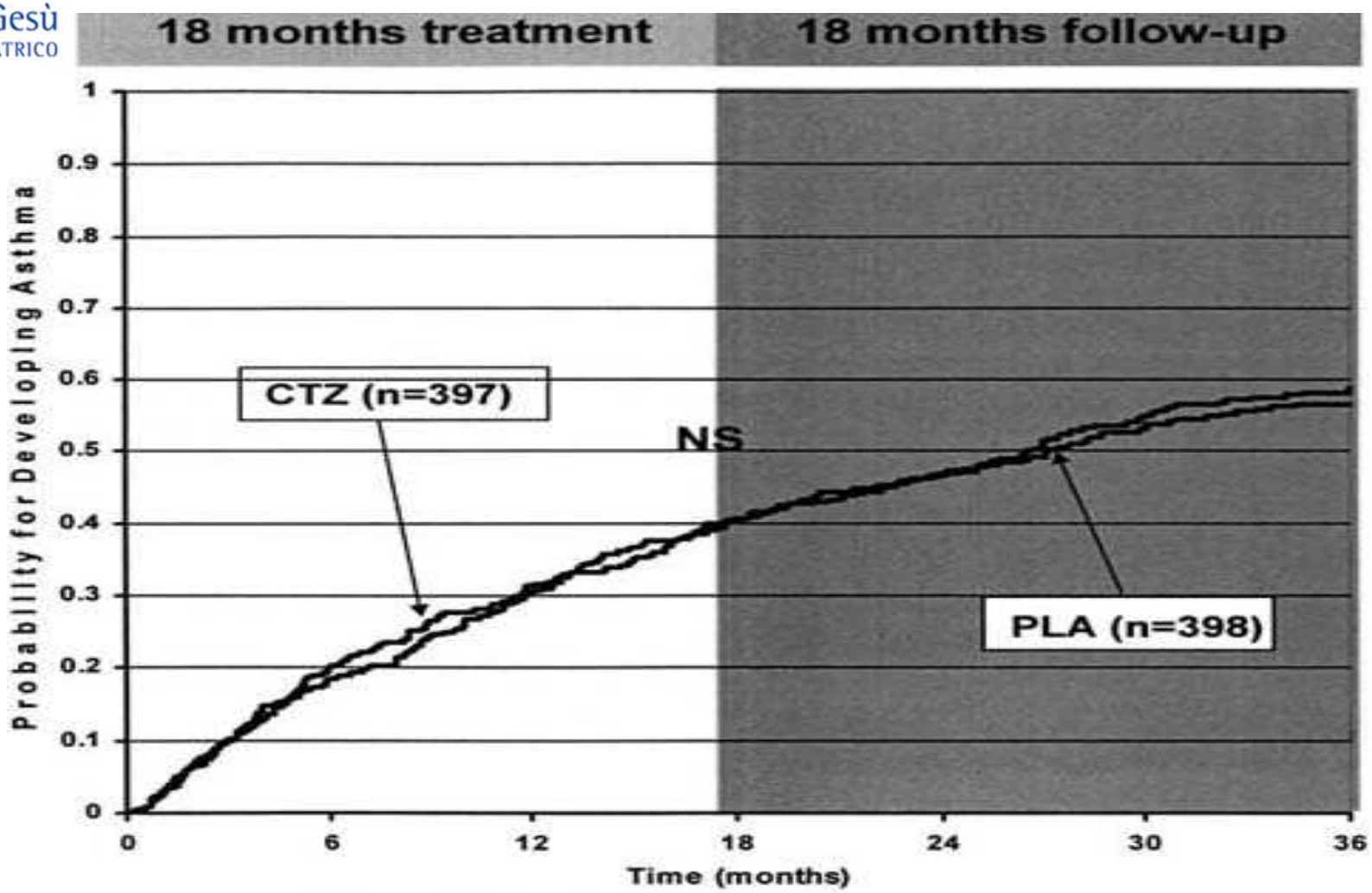

CTZ = cetirizine treatment group
PLA = placebo treated group
n = number of infants in each group

Warner JO Allergy Clin Immunol 2001;108:929-37

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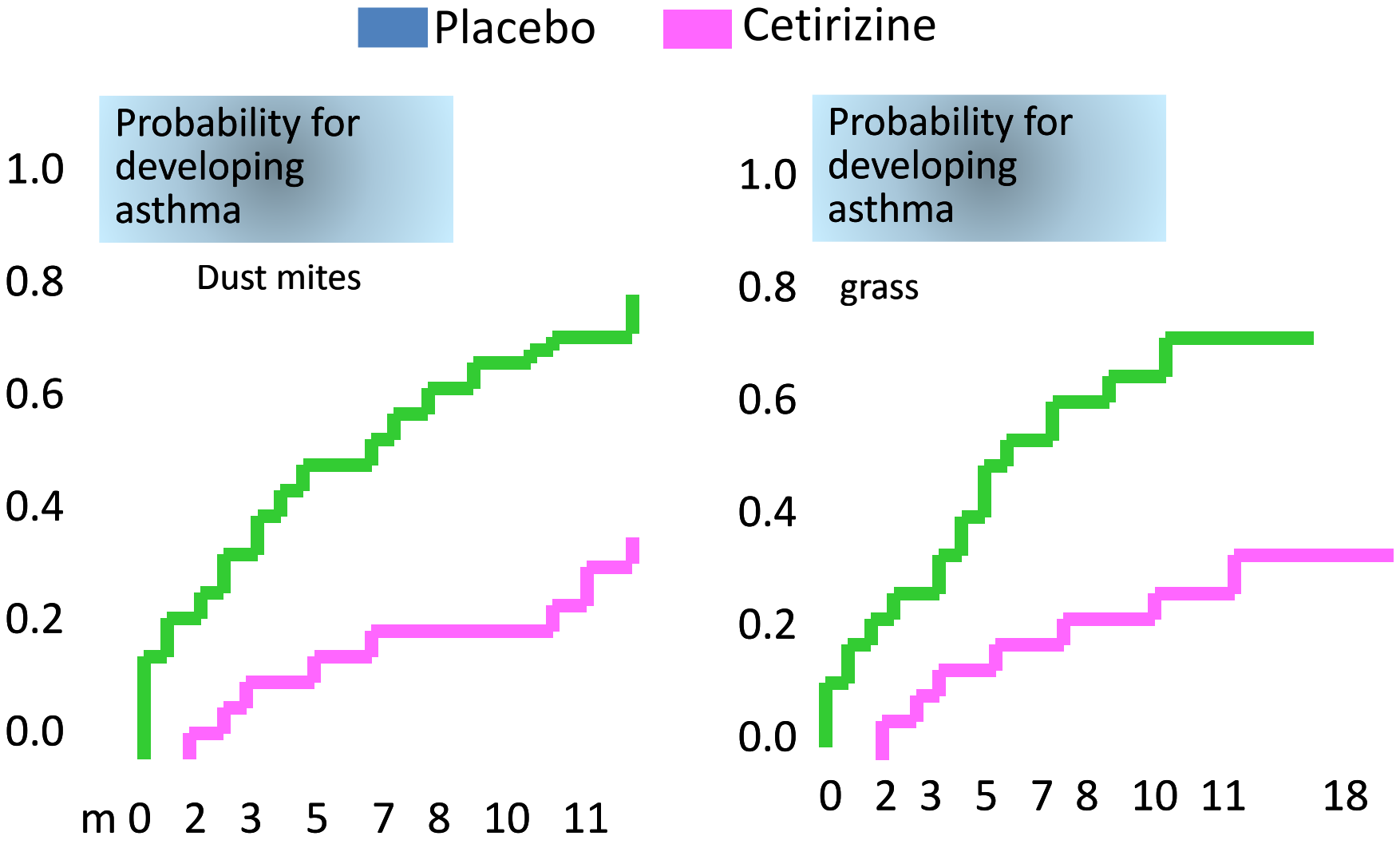
ETAC: early treatment of the atopic child



Warner JO Allergy Clin Immunol 2001;108:929-37

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Early prevention of allergy and asthma in children (EPAAC)

Children aged 12 - 24 months, no asthma
Family history of atopy
Early AD
Sensitised to HDM, Grass
Outcome: time to onset of asthma.

Patients: 2106

Hypothesis: asthma can be delayed by levocetirizine in children with atopic dermatitis sensitized to specific aeroallergens.

de Benedictis FM. The allergic sensitization in infants with atopic eczema from different countries. Allergy. 2009;64:295-303

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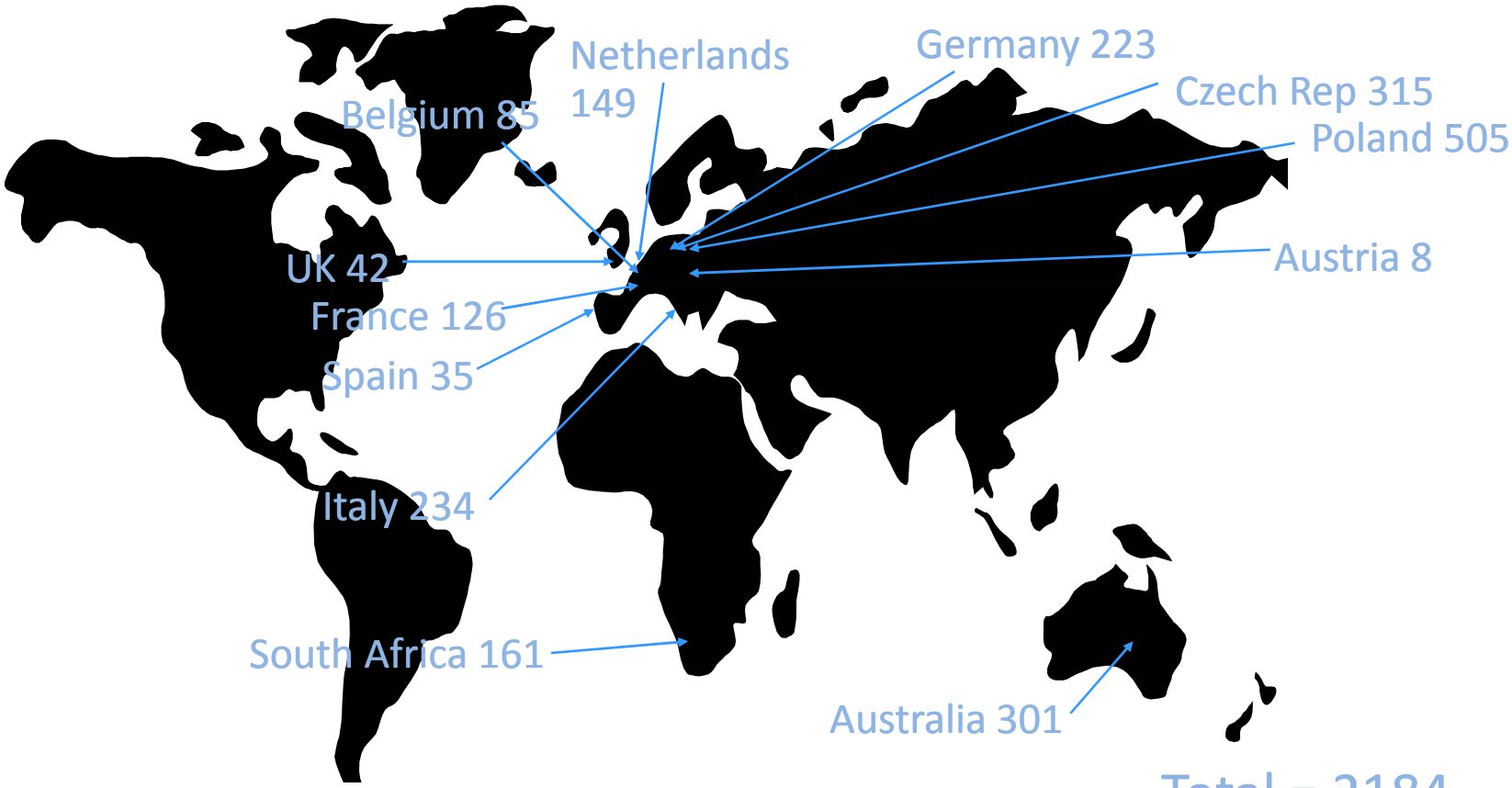
Early prevention of allergy and asthma in children (EPAAC)



de Benedictis FM. The allergic sensitization in infants with atopic eczema from different countries. Allergy. 2009;64:295-303

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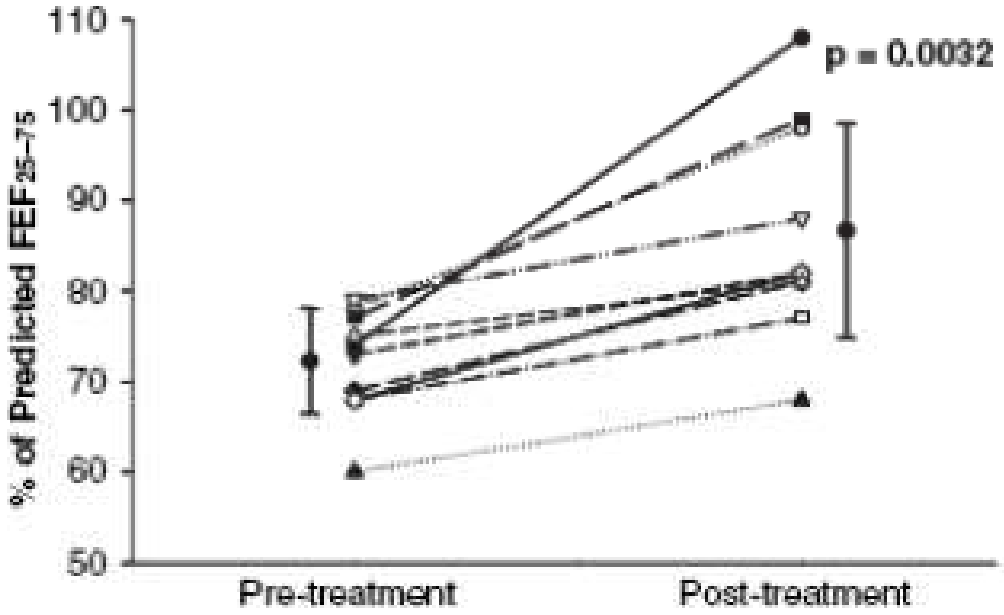
Do children with atopic dermatitis progress to asthma?

- This concept formed the very basis of the Early Treatment of the Atopic Child study and EPAAC

- The study failed to show any benefit from the antihistamine cetirizine in preventing subsequent asthma in children with early eczema.

Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immuno 2006;118:209-13

Nasal corticosteroids improve the pulmonary function tests of AR children with impaired lung function



FEF_{25-75} of children with persistent allergic rhinitis and abnormal pulmonary function at baseline and after treatment with daily nasal corticosteroid (3 months) and loratidine (10 days).

Kessel A. Abnormal spirometry in children with persistent allergic rhinitis due to mite sensitization: the benefit of nasal corticosteroids. Pediatr Allergy Immunol. 2008;19:61-6

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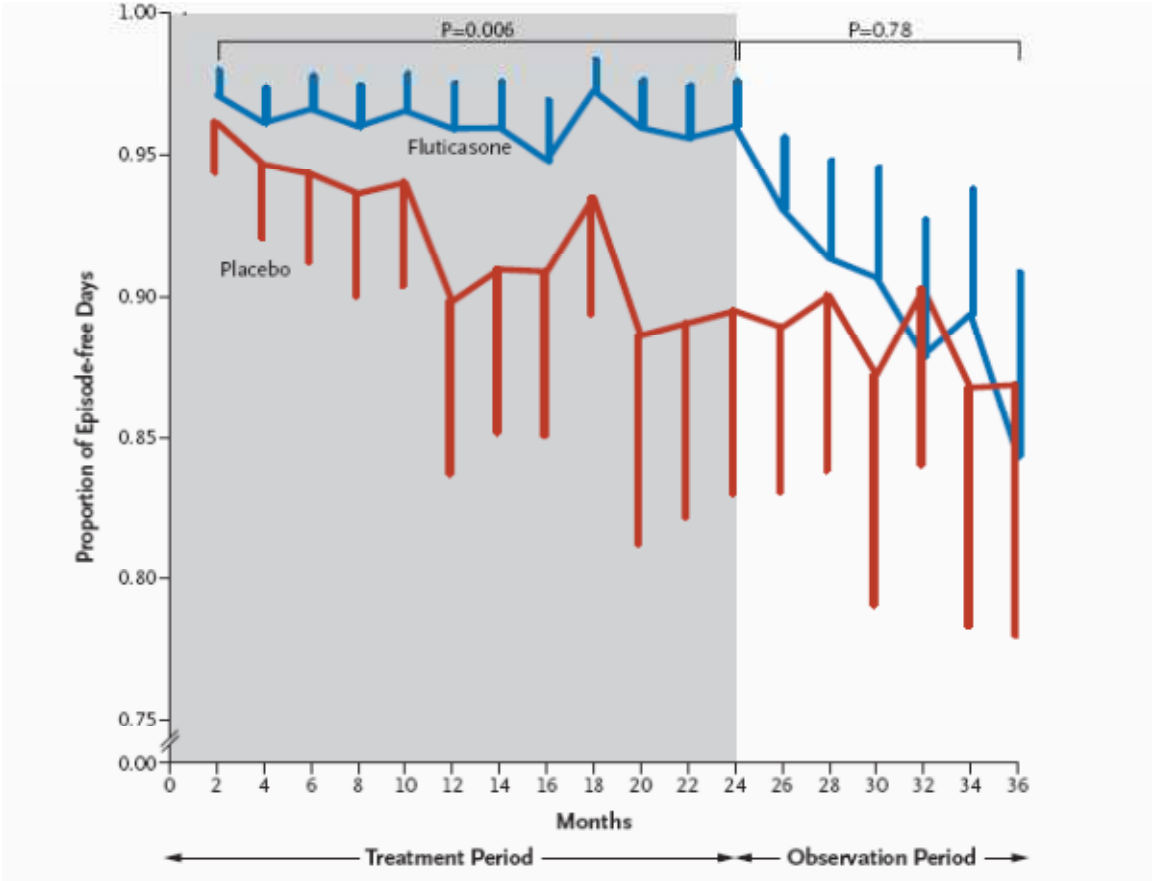
ICS control but do not cure the disease



285 preschool kids with wheeze and high asthma risk Index

Guilbert, NEJM 2006; 354:1985-97

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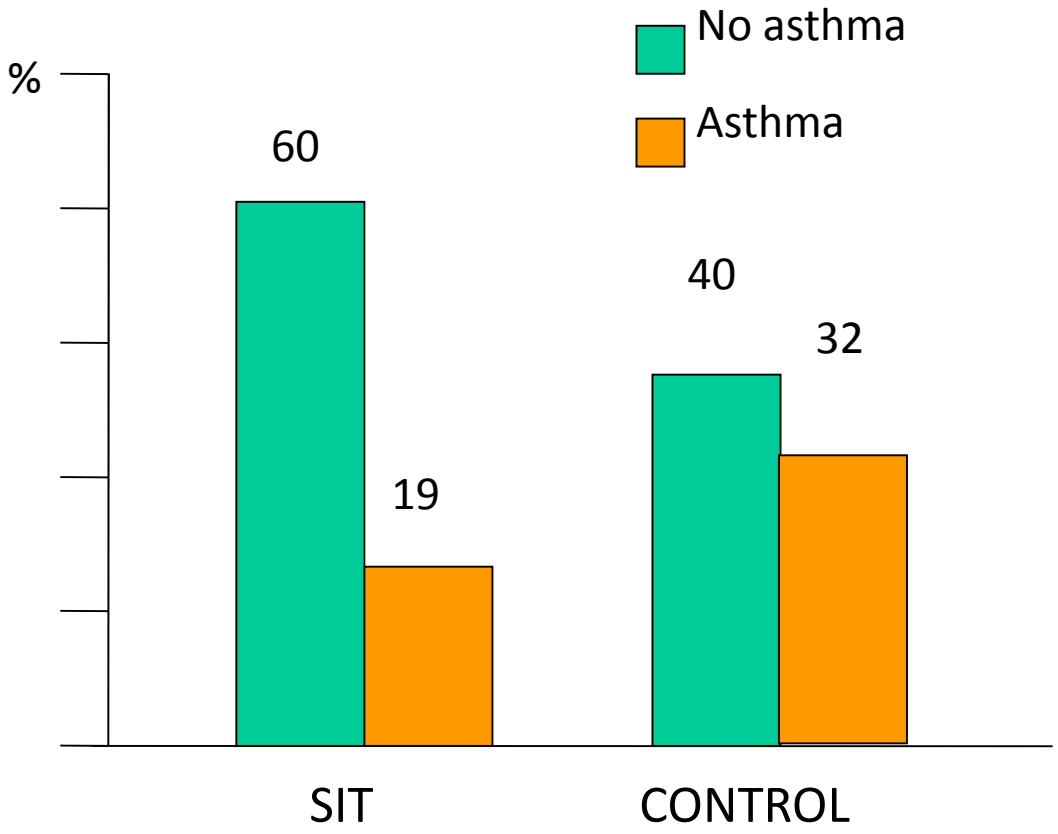
Development of asthma in children with allergic rhinitis



205 children with rhinitis

age: 6-14 yrs

grass or birch allergy

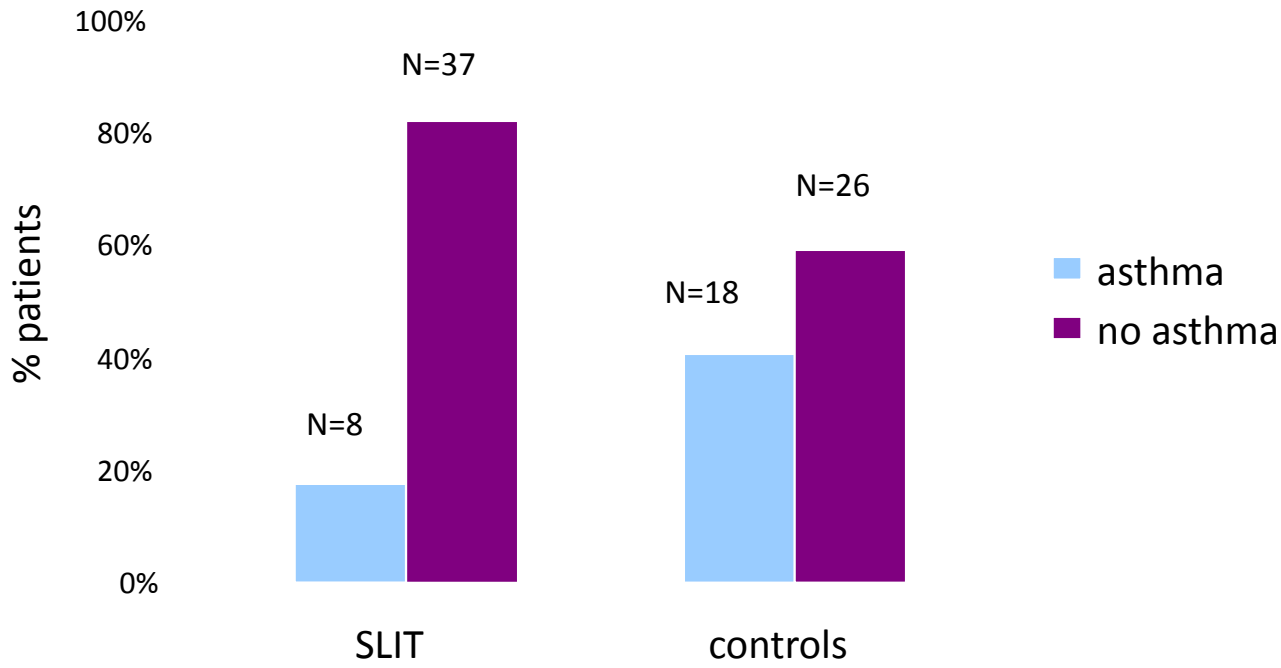
3 yrs immunotherapy

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

SLIT reduces asthma odds

Children with AR, followed-up for three years

Odds ratio 3.60



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

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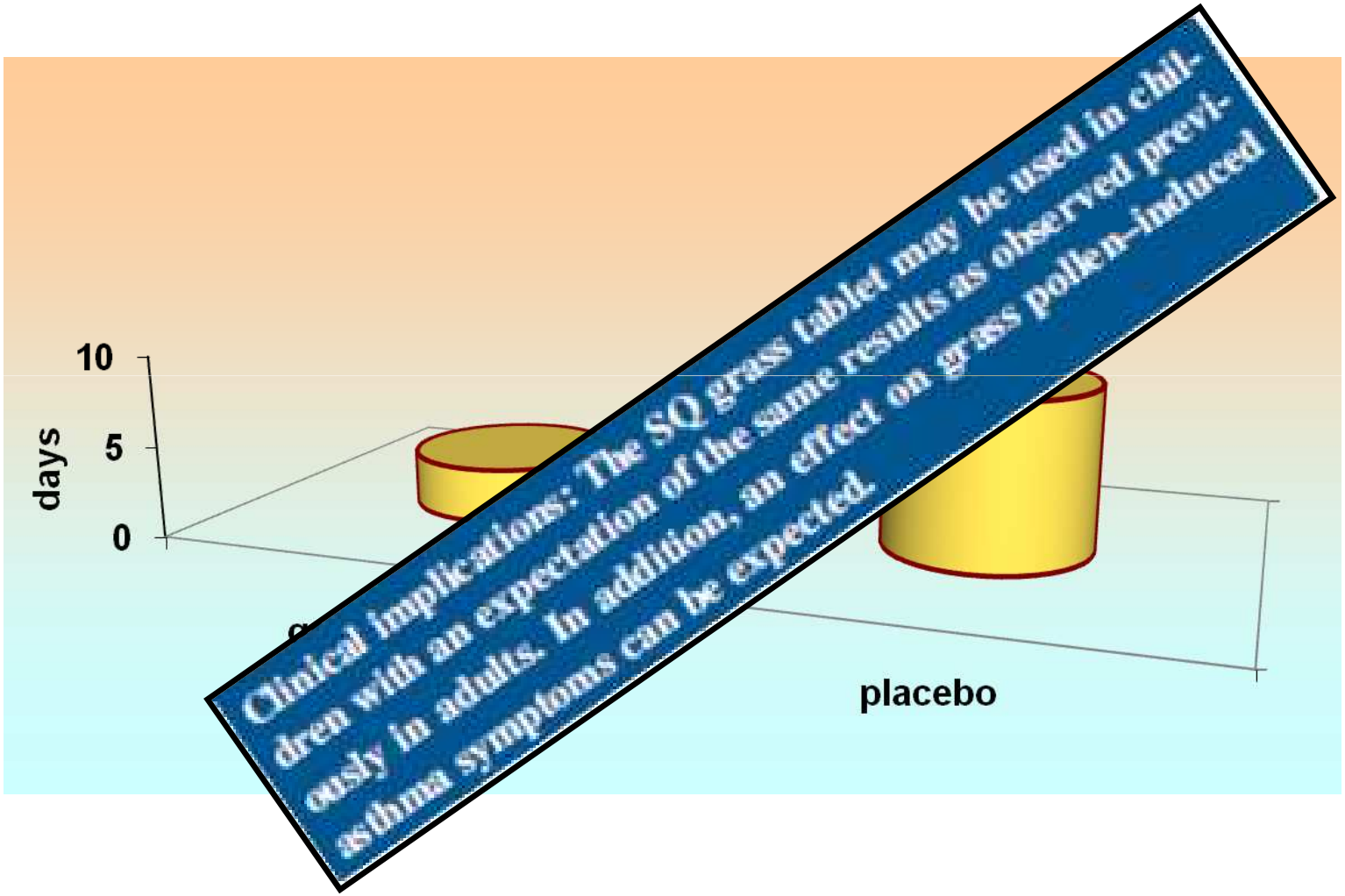
Asthma symptoms days in children with allergic rhinitis



Bufe A. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy J Allergy Clin Immunol 2009;123:167-73

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SIT and SLIT in children

- long-term benefit up to 12 years after its discontinuation
- Can prevent the onset of new sensitizations
- Can reduce the evolution from rhinitis to asthma
- SLIT shows long-lasting effects
- SLIT interferes with the progression of rhinitis towards asthma

Pajno GB. Sublingual immunotherapy: the optimism and the issues.
J Allergy Clin Immunol. 2007;119:796-801

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Wheezing, asma o....?

La rinite allergica è fattore di sviluppo per l'asma

Il controllo clinico previene la marcia allergica

Qual è la strategia terapeutica ottimale in pediatria?

Trattare asma e rinite insieme

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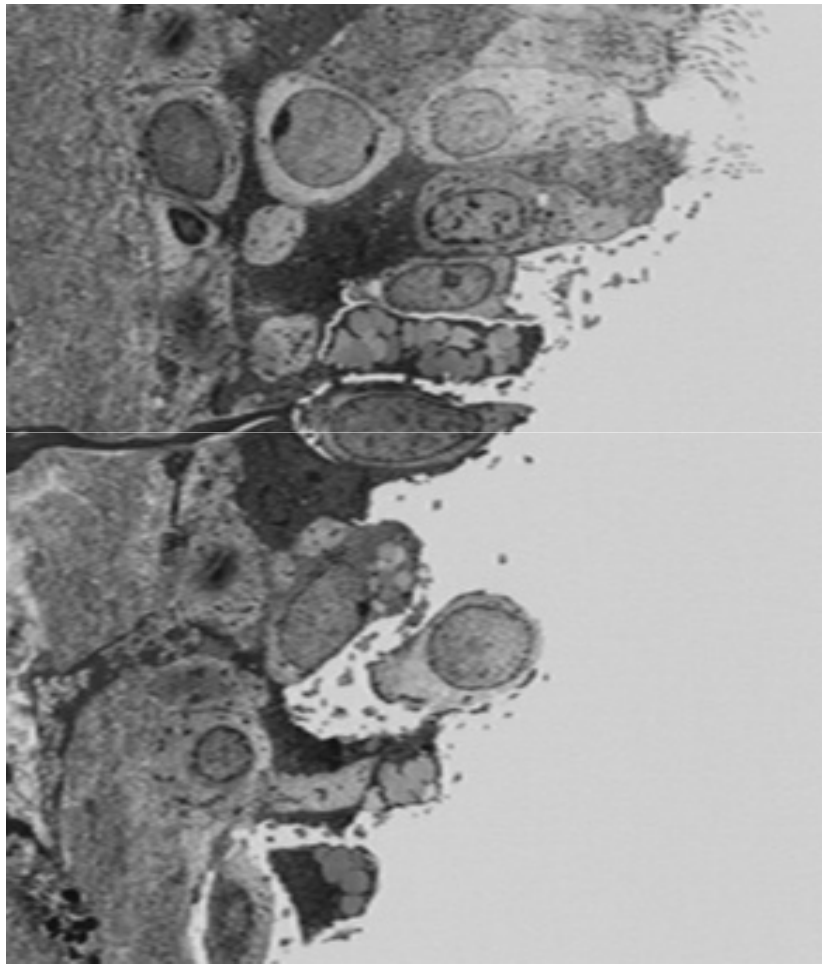
Epithelial repair following steroid treatment



Before

After

P Howarth, 1999

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Fluticasone per via inalatoria orale e intranasale in pazienti con asma e rinite: efficacia e tollerabilità

Effetto degli steroidi nasali sull'asma durante l'esposizione a pollini

a. Fluticasone intranasale 200 mcg/die
b. Fluticasone inalatorio 250 mcg x 2/die
c. a+b
d. Placebo

Sintomi nasali:	**a > b,c,d**
PEF, FEV1:	**b > a,c,d**
Mch PD20:	**b > a,c,d**
Eosinofili nell'escreato:	**b > a,c,d**

⇒ **Se ci soino rinite ed asma, servono sia FC nasale che FC inalatorio**

Dahl R. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. Allergy. 2005;60:875-81

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Steroidi e crescita

Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults

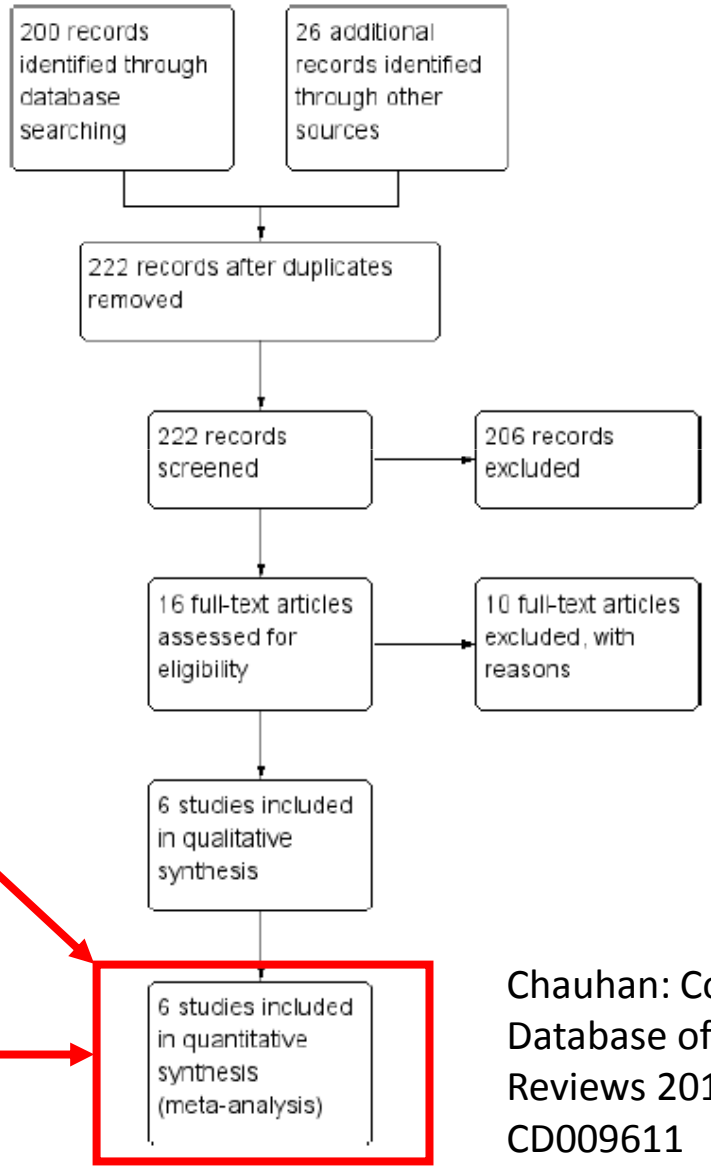
Paediatic studies:

Papi: Allergy 2009;64:1463–71

Turpeinen: Arch Dis Child 2008;93: 654–9.

Zeiger: NEJM 2011;365:1990

Martinez: Lancet 2011;377:650–7



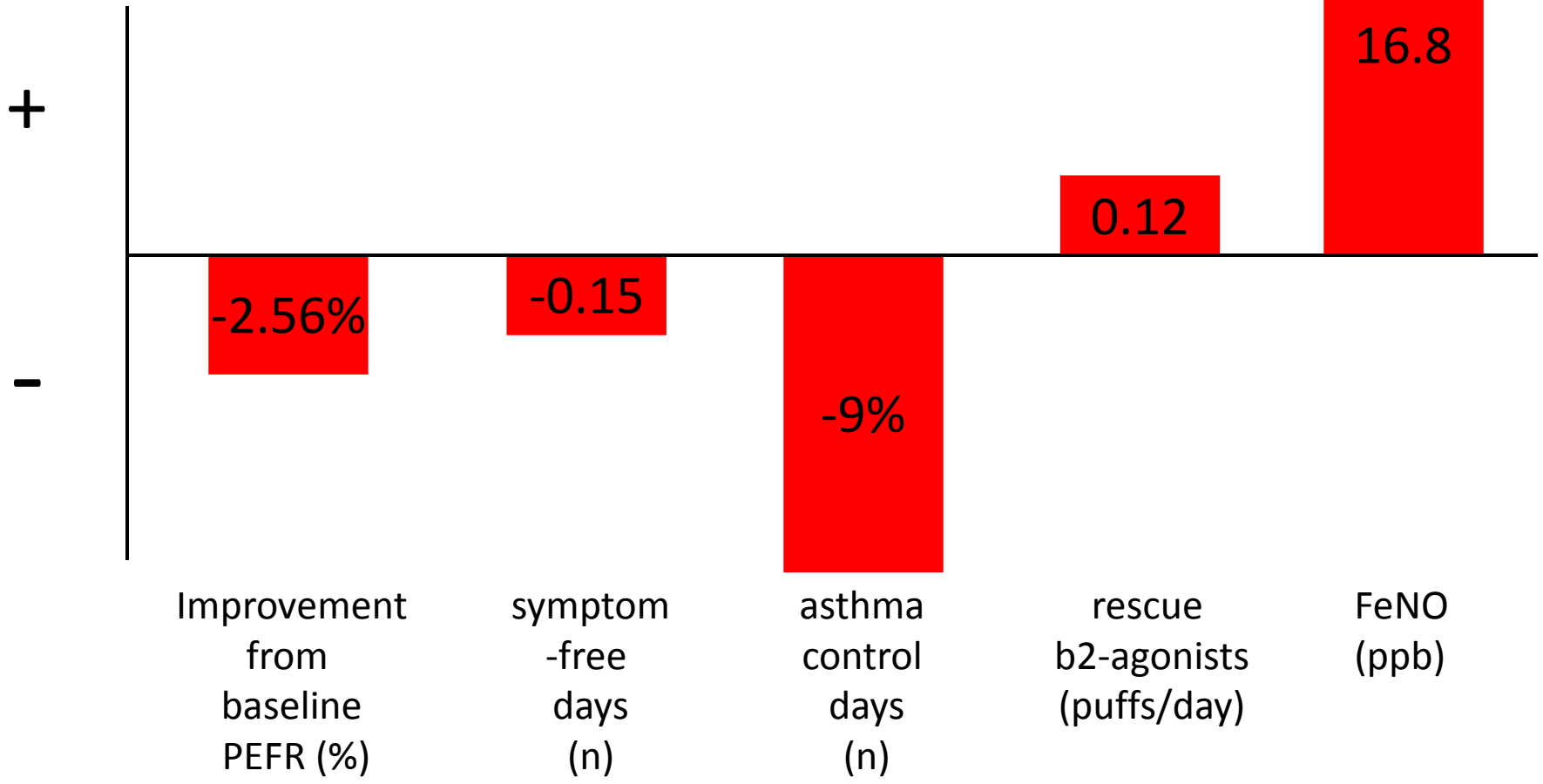
The duration of intervention varied from 12 to 52 weeks

Chauhan: Cochrane Database of Systematic Reviews 2012, 12: CD009611

Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults

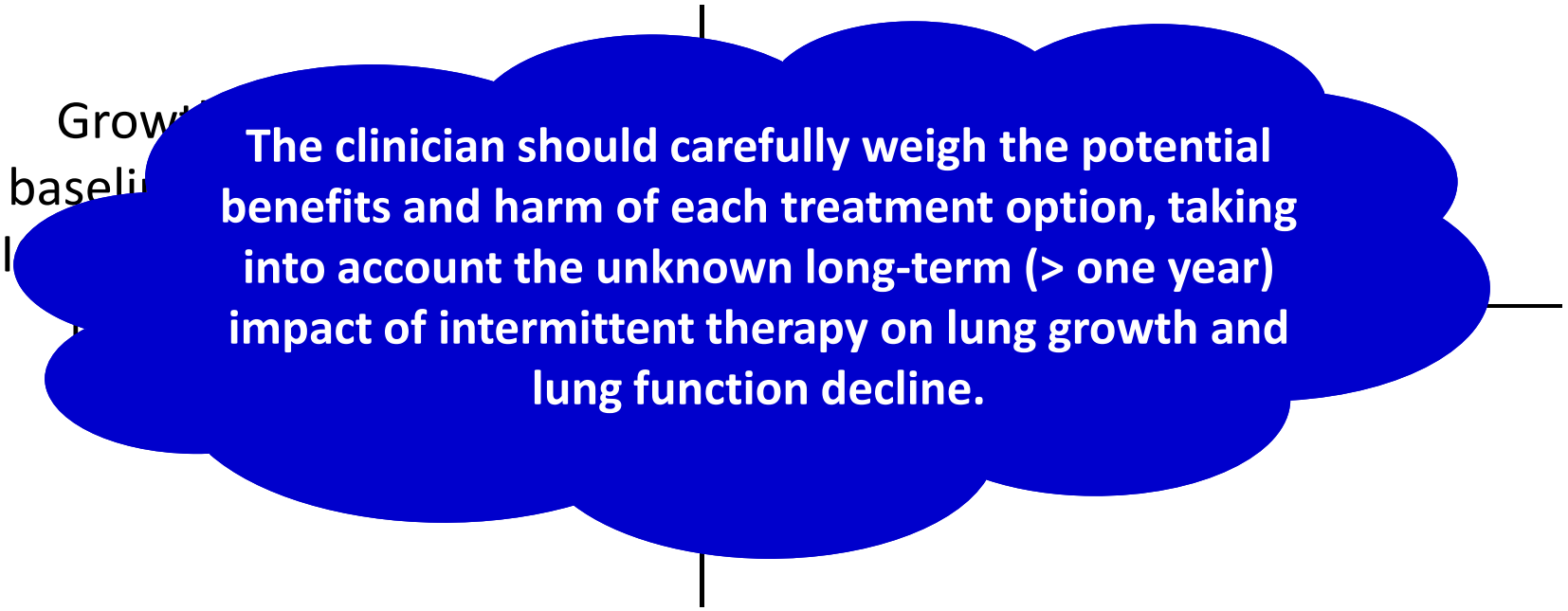
Intermittent ICS group vs Daily ICS group: significant differences

Chauhan: Cochrane Database of Systematic Reviews 2012, 12: CD009611



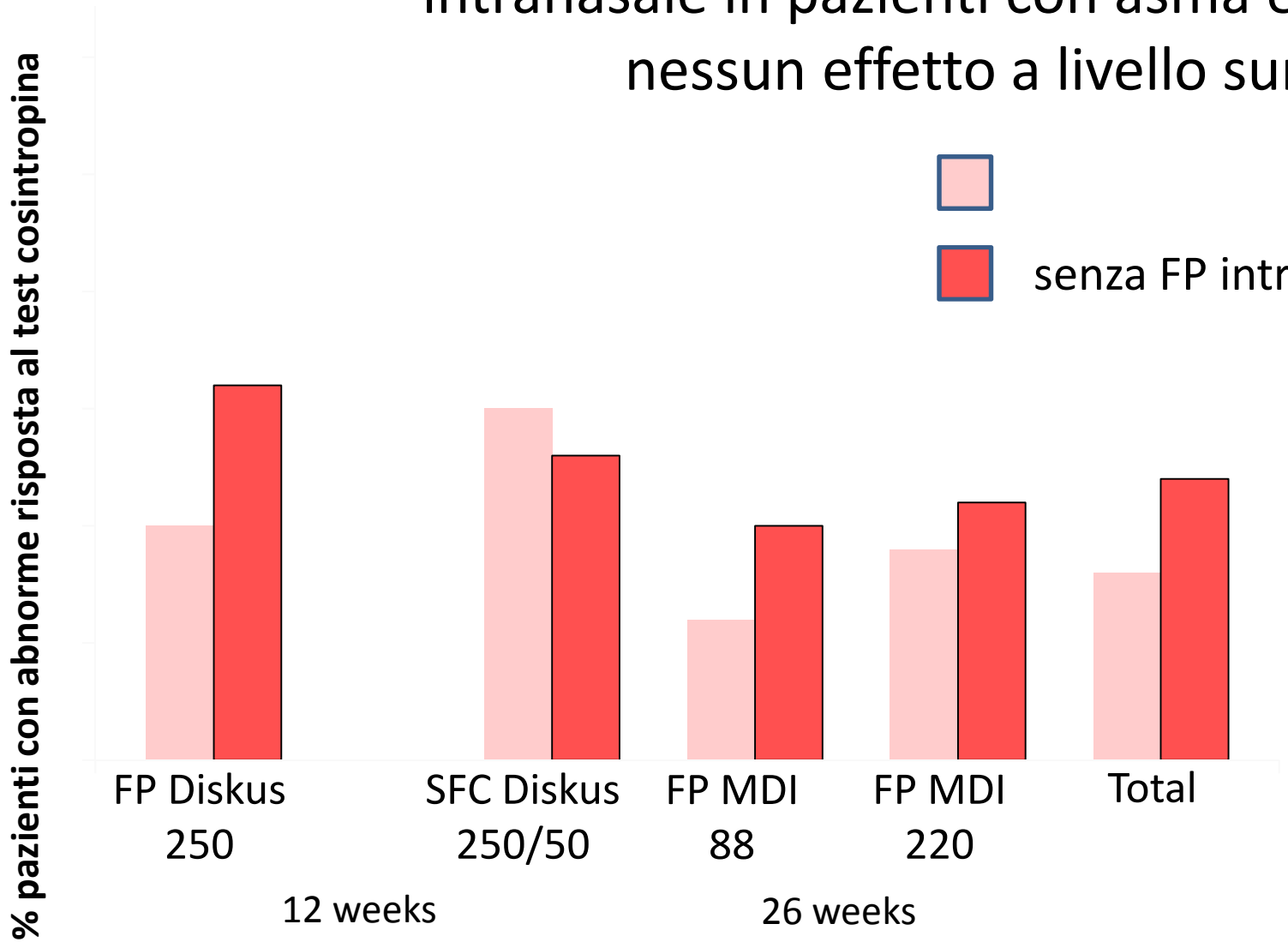
Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults

Intermittent ICS group vs Daily ICS group: significant differences



Chauhan: Cochrane Database of Systematic Reviews 2012, 12: CD009611

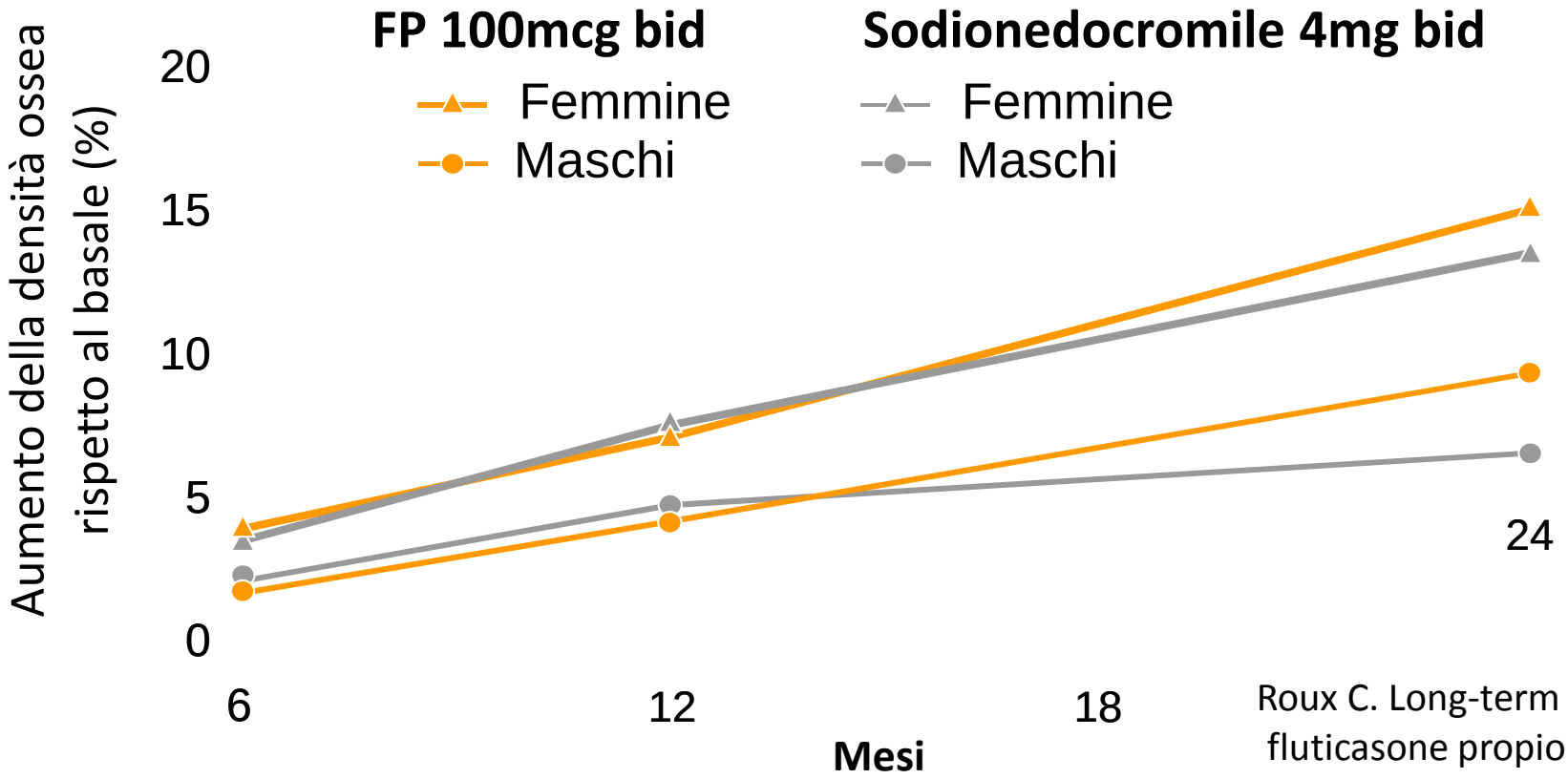
Tollerabilità di Fluticasone per via inalatoria orale + intranasale in pazienti con asma e rinite: nessun effetto a livello surrenale



Sheth KK. Concurrent use of intranasal and orally inhaled fluticasone propionate does not affect hypothalamic-pituitary-adrenal-axis function. Allergy Asthma Proc. 2004;25:115-20

Fluticasone: nessun effetto sulla densità ossea dopo due anni di trattamento

Densitometria ossea Spina lombare



- 174 pz pediatrici (6-14 aa), FP 200mcg bid per 2 anni
- Nessuna differenza vs placebo per crescita e densità ossea misurata a livello della spina lombare e della testa del femore

Roux C. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics. 2003;111:e706-13

Fluticasone in pediatria: tollerabilità asse ipotalamo-ipofisi-surrene

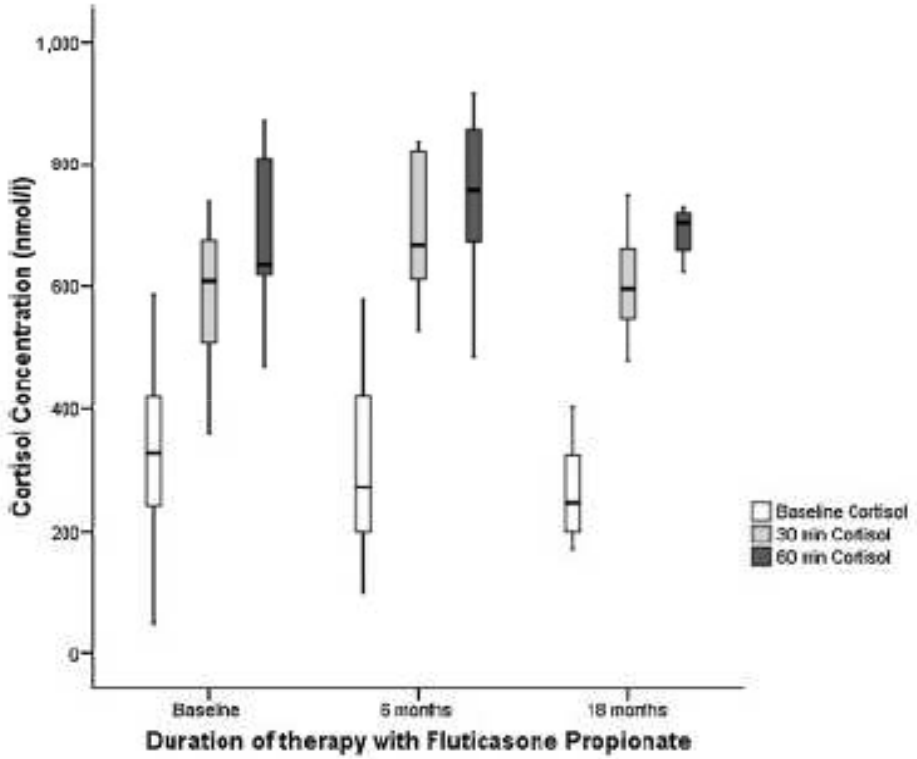


Fig. 1. Median (IQR) cortisol response to Synacthen (fasting, 30 and 60 min) at baseline and following 6 and 18 months FP treatment.

Nessuna differenza tra basale (prima della terapia) vs 6 e 18 mesi di trattamento con FP nella riserva surrenale (capacità di corticotropina sintetica di stimolare il rilascio di cortisolo dal surrene)

Illes R. A longitudinal assessment of the effect of inhaled fluticasone propionate therapy on adrenal function and growth in young children with asthma. Pediatr Pulmonol. 2008;43:354-9

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Conclusions

- Rhinitis is associated with subclinical signs of asthma
- ⇨ the most mild form of atopic march!
- Identifying early childhood rhinitis & asthma phenotypes may represent a more robust measure of identification
- Treatment of allergic rhinitis with allergen immunotherapy modifies the risk of developing asthma
- For the control of the disease, continuous topical steroid is better-fitting
- Other preventive strategies?