**X SESSIONE**
CONSENSUS
CORTICOSTEROIDI INALATORI IN ETÀ EVOLUTIVA
Presidente: *Mazzia Duse*
Moderatori: *Gaetano Bollaro, Mario La Rosa*

# ASMA

**Carlo Capristo**

Università degli Studi della Campania *Luigi Vanvitelli*

DIPARTIMENTO DELLA DONNA DEL BAMBINO E DI CHIRURGIA GENERALE E SPECIALISTICA
RESPONSABILE U.O.S.D. NEONATOLOGIA

# Aggiornamento del Progetto Asma Italia 2017

## Coordinatori: Pierluigi Paggiaro, Elena Bacci

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| Capitolo 2. Epidemiologia ed impatto socio-economico dell'asma | Stefania La Grutta, Giuseppe Verlato, Giovanni Viegi |
| Capitolo 3. Fattori di rischio per asma | Gabriella Guarnieri, Gennaro Liccardi |
| Capitolo 4. Fisiopatologia, patogenesi e anatomia patologica | Cecilia Calabrese, Alessandro Celi, Girolamo Pelaia, Nicola Scichilone |
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| Capitolo 8. Prevenzione e riduzione dei fattori scatenanti dell'asma | Francesca Santamaria, Alessandro Vatrella |
| Capitolo 9. La terapia farmacologica dell'asma nell'adulto | Bianca Beghè, Stefano Del Giacco, Luigi Macchia e Pierluigi Paggiaro |
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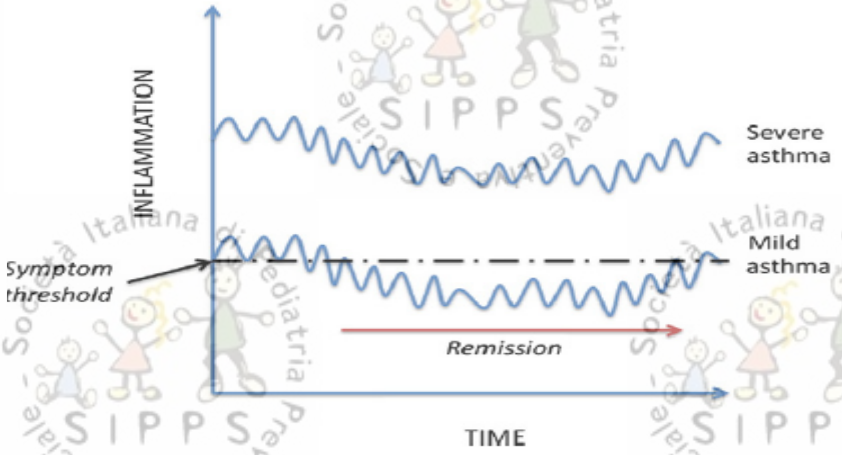
Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

2011

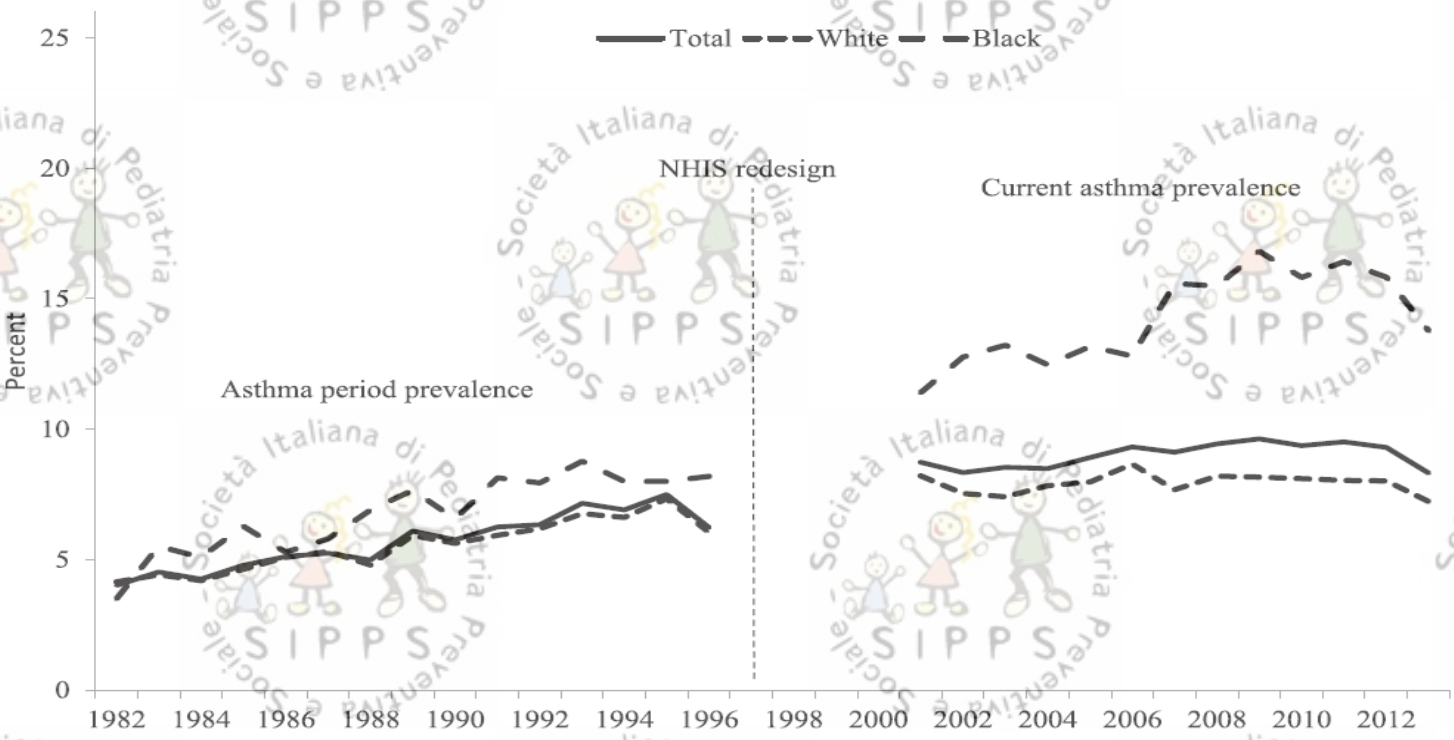
# Remission of asthma: The next therapeutic frontier?




John W. Upham

# Trend in asthma prevalence by race: United States, 1982–2013.

children ages 0 to 17 years

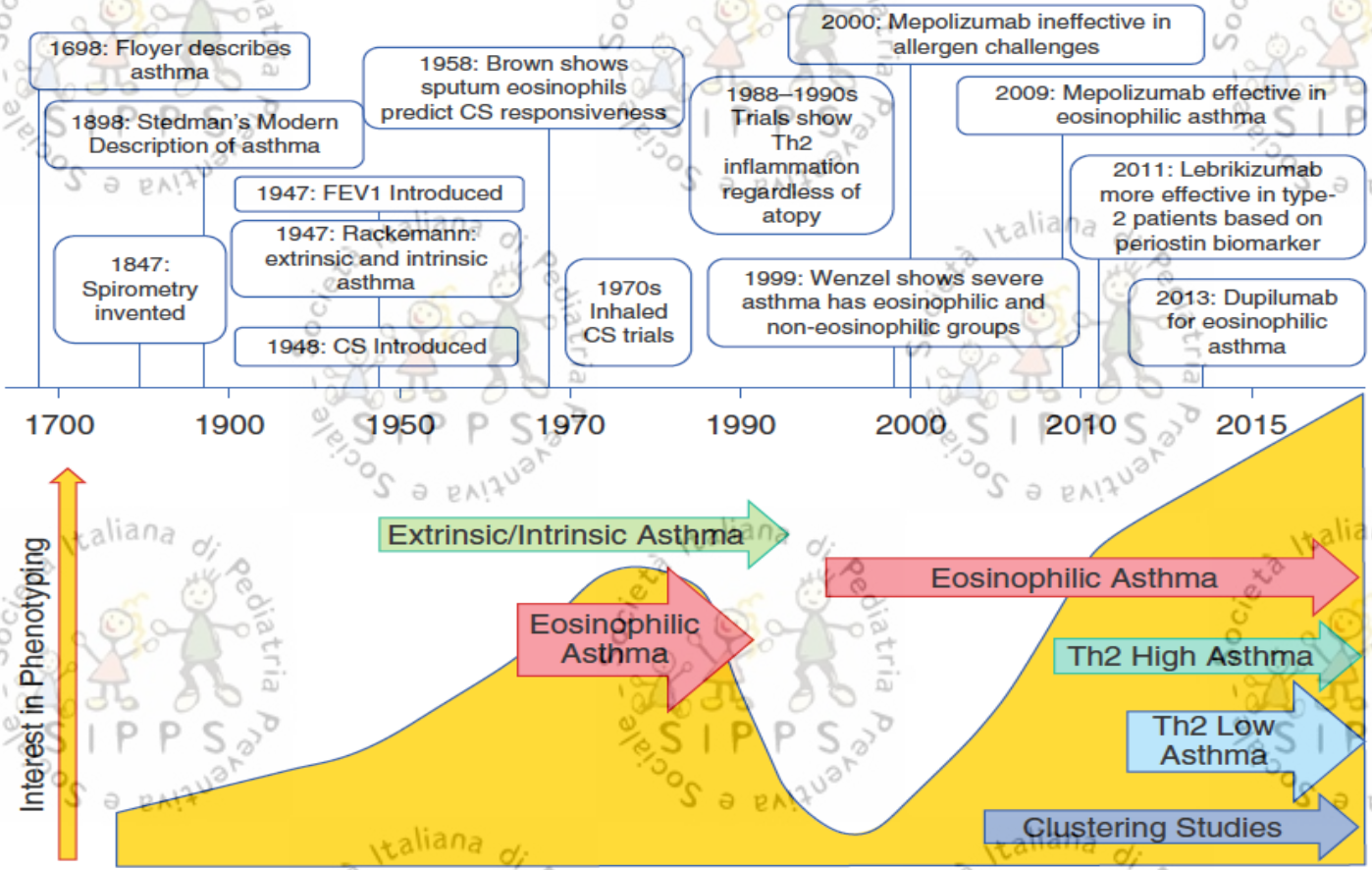



Akinbami L J, Pediatrics. 2016

# Evolving Concepts of Asthma

**A timeline showing major events in the understanding of asthma and phenotyping.**

*CS=corticosteroids*




Gauthier M, AJRCCM 2015

# PAPERS AND ORIGINALS

## Beclomethasone Dipropionate: A New Steroid Aerosol for the Treatment of Allergic Asthma

H. MORROW BROWN, G. STOREY, W. H. S. GEORGE

*British Medical Journal*, 1972, 1, 585-590

**Summary**

**Beclomethasone dipropionate was used in pressurized aerosols for the treatment of 60 cases of chronic allergic asthma for up to 15 months. Twenty-eight out of 37 cases were transferred to this treatment after being dependent on oral steroids for up to 16 years. Nineteen out of 23 other asthmatics not dependent on steroids were also completely controlled. No biochemical evidence of adrenal suppression was found. Steroid withdrawal symptoms were often a problem, suggesting absence of systemic absorption. The precise mode of action and metabolic fate of this corticosteroid are not yet known.**

typical steroid side effects was noted by Siegel *et al.* (1964), Novey and Beall (1965), and Toogood and Lefcoe (1965). Biochemical evidence of adrenal suppression was reported by Linder (1964). Systemic absorption of dexamethasone thus proved an insuperable problem which rendered administration of this steroid by aerosol rather pointless.

Beclomethasone dipropionate, which has already been used for some years as a topical ointment for eczema, does not suffer from this defect. This compound was used in aerosol form for the present trial.

### Case Selection

Sixty patients were selected for the trial from both National

# Inhaled Corticosteroids in Lung Diseases

TABLE 2. COMPARATIVE DAILY DOSAGES OF INHALED CORTICOSTEROIDS*

| Corticosteroid | Low Daily Dose (μg, *Child*†/*Adult*) | Medium Daily Dose (μg, *Child*†/*Adult*) | High Daily Dose (μg, *Child*†/*Adult*) |
|---|---|---|---|
| BDP | | | |
| HFA MDI | 80–160/80–240 | >160–320/>240–480 | >320/>480 |
| BUD | | | |
| DPI | 180–360/180–540 | >360–720/>540–1,080 | >720/>1,080 |
| Nebules | 500/UK | 1,000/UK | 2,000/UK |
| CIC | 80–160/160–320 | >160–320/>320–640 | >320/>640 |
| FLU | | | |
| HFA MDI | 160/320 | 320/320–640 | >640/>640 |
| FP | | | |
| HFA MDI | 88–176/88–264 | >176–352/>264–440 | >352/>440 |
| DPIs | 100–200/100–300 | >200–400/>300–500 | >400/>500 |
| MF, DPI | 110/220 | 220–440/440 | >440/>440 |

# Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012)

*Stefan Ebmeier, Darmiga Thayabaran, Irene Braithwaite, Clément Bénamara, Mark Weatherall, Richard Beasley*

## Summary

**Background** International time trends in asthma mortality have been strongly affected by changes in management and in particular drug treatments. However, little is known about how asthma mortality has changed over the past decade. In this study, we assessed these international trends.

**Methods** We collated age-standardised country-specific asthma mortality rates in the 5–34 year age group from the online WHO Mortality Database for 46 countries. To be included in the analysis, we specified that a country must have 10 years of complete data in the WHO Mortality Database between 1993 and 2012. In the absence of consistent and accurate asthma prevalence and prescribing data, we chose to use a locally weighted scatter plot smoother (LOESS) curve, weighted by the individual country population in the 5–34-year age group to show the global trends in asthma mortality rates with time.

**Findings** Of the 46 countries included in the analysis of asthma mortality, 36 were high-income countries, and 10 were middle-income countries. The LOESS estimate of the global asthma mortality rate was 0·44 deaths per 100 000 people (90% CI 0·39–0·48) in 1993 and 0·19 deaths per 100 000 people (0·18–0·21) in 2006. Despite apparent further reductions in some countries and regions of the world, there was no appreciable change in global asthma mortality rates from 2006 through to 2012, when the LOESS estimate was also 0·19 deaths per 100 000 people (0·16–0·21).

**Interpretation** The trend for reduction in global asthma mortality observed since the late 1980s might have stalled, with no appreciable difference in a smoothed LOESS curve of asthma mortality from 2006 to 2012. Although better implementation of established management strategies that have been shown to reduce mortality risk is needed, to achieve a further substantive reduction in global asthma mortality novel strategies will also be required.

**Funding** The Medical Research Institute of New Zealand, which is supported by Health Research Council of New Zealand Independent Research Organisation.

*Lancet* 2017; 390: 935–45

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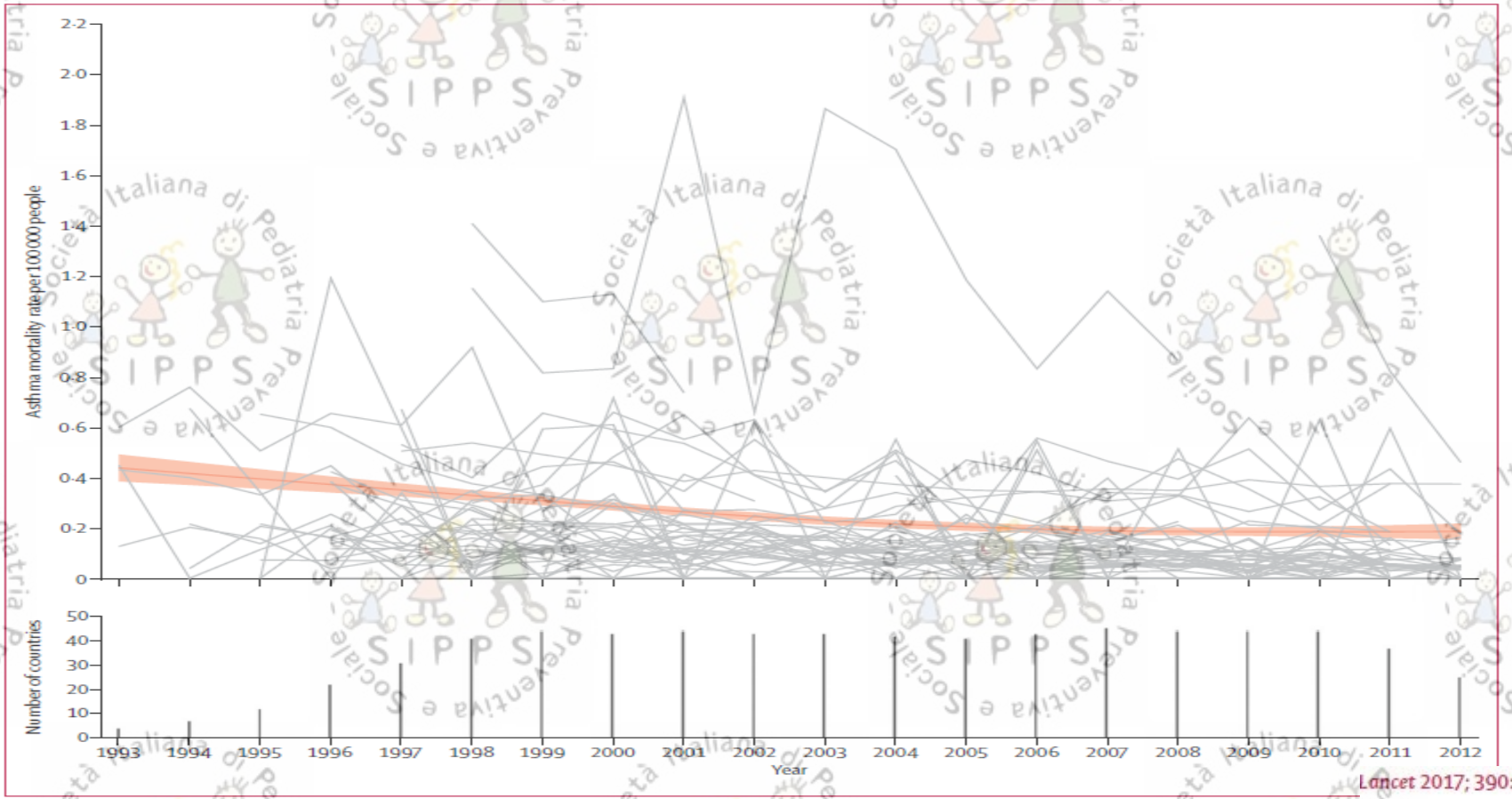
**Medical Research Institute of New Zealand, Wellington, New Zealand** (S Ebmeier BMBCh, D Thayabaran BMBCh, I Braithwaite PhD, C Bénamara MSc, Prof R Beasley DSc) **and Department of Medicine, University of Otago Wellington, Wellington, New Zealand** (Prof M Weatherall MBChB)

Correspondence to: Prof Richard Beasley, Medical Research Institute of New Zealand, Private Bag 7902, Wellington 6242, New Zealand **richard.beasley@mrinz.ac.nz**

# Age-standardised asthma mortality rates for the 5–34-year age group in 46 countries, for the years 1993–2012

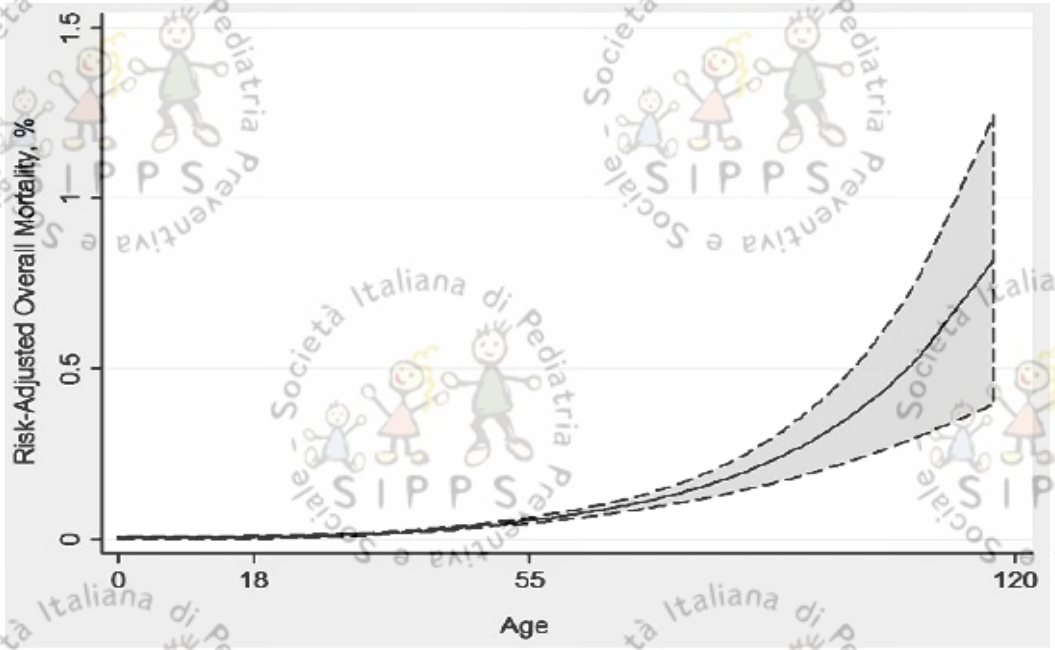



*Lancet* 2017; 390: 935–45

# Age-related differences in clinical outcomes for acute asthma in the United States, 2006-2008

Chu-Lin Tsai, MD, ScD,[a] Wen-Ya Lee, MS, MPH,[a] Nicola A. Hanania, MD, MS,[b] and Carlos A. Camargo, Jr, MD, DrPH[c] *Houston, Tex, and Boston, Mass*

Risk-adjusted probabilities of overall mortality as a function of age. The 95% CIs are indicated by the *dashed lines*.




asthma-related deaths per year

- 37 in children
- 204 in younger adults
- 903 in older adults.

J ALLERGY CLIN IMMUNOL
VOLUME 129, NUMBER 5

2012

# Risk factors for asthma: is prevention possible?

*Richard Beasley, Alex Semprini, Edwin A Mitchell*

Asthma is one of the most common diseases in the world, resulting in a substantial burden of disease. Although rates of deaths due to asthma worldwide have reduced greatly over the past 25 years, no available therapeutic regimens can cure asthma, and the burden of asthma will continue to be driven by increasing prevalence. The reasons for the increase in asthma prevalence have not been defined, which limits the opportunities to develop targeted primary prevention measures. Although associations are reported between a wide range of risk factors and childhood asthma, substantiation of causality is inherently difficult from observational studies, and few risk factors have been assessed in primary prevention studies. Furthermore, none of the primary prevention intervention strategies that have undergone scrutiny in randomised controlled trials has provided sufficient evidence to lead to widespread implementation in clinical practice. A better understanding of the factors that cause asthma is urgently needed, and this knowledge could be used to develop public health and pharmacological primary prevention measures that are effective in reducing the prevalence of asthma worldwide. To achieve this it will be necessary to think outside the box, not only in terms of risk factors for the causation of asthma, but also the types of novel primary prevention strategies that are developed, and the research methods used to provide the evidence base for their implementation. In the interim, public health efforts should remain focused on measures with the potential to improve lung and general health, such as: reducing tobacco smoking and environmental tobacco smoke exposure; reducing indoor and outdoor air pollution and occupational exposures; reducing childhood obesity and encouraging a diet high in vegetables and fruit; improving feto-maternal health; encouraging breastfeeding; promoting childhood vaccinations; and reducing social inequalities.

*Lancet* 2015; 386: 1075–85

See Editorial page 1014

This is the first in a Series of two papers about Asthma

Medical Research Institute of New Zealand, Wellington, New Zealand (Prof R Beasley DSc, A Semprini MBBS); and Department of Paediatrics, Child and Youth Health, University of Auckland, Auckland New Zealand (Prof E A Mitchell DSc)

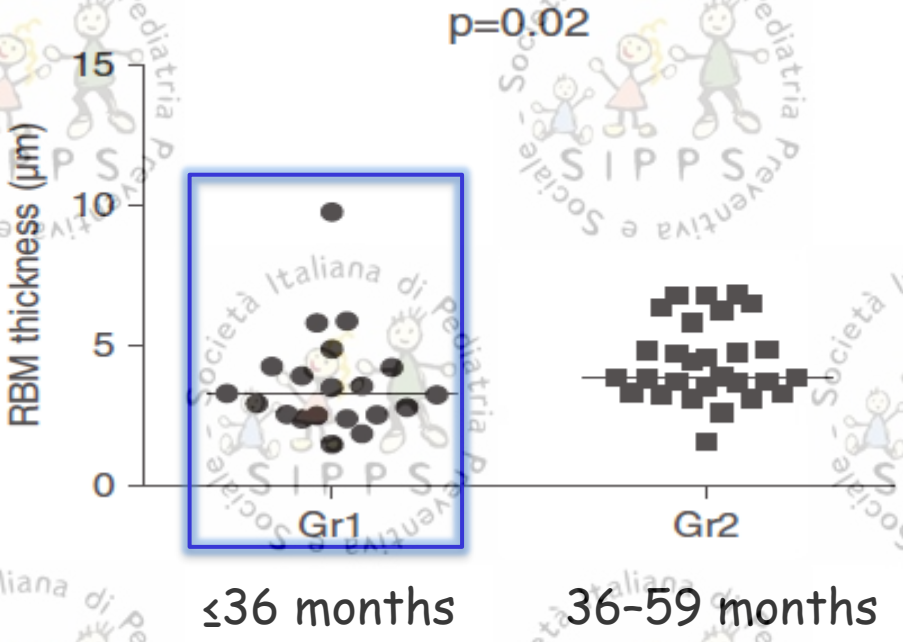
Correspondence to: Prof Richard Beasley, Medical Research Institute of New Zealand, Wellington 6242, New Zealand
Richard.Beasley@mrinz.ac.nz

# Airway Remodeling in Preschool Children with Severe Recurrent Wheeze.

*Lezmi G, AJRCCM 2015;192:164-171*

- ✓ Flexible bronchoscopy in 2 groups of preschoolers with severe recurrent wheeze: group 1, ≤36 months (n = 20); group 2, 36–59 months (n = 29).
- ✓ Airway inflammation, reticular basement membrane (RBM) thickness, airway smooth muscle (ASM), mucus gland area, vascularity, and epithelial integrity.
- ✓ 21 schoolchildren with severe asthma (group 3, 5–11.2 yr).

**RBM thickness was lower in group 1 than in group 2 (3.3 vs. 3.9 µm; *p=0.02* )**



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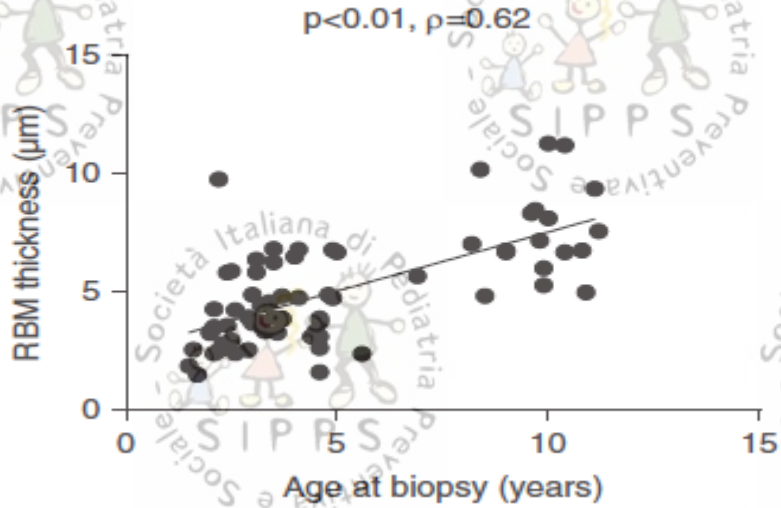
**RBM was correlated with age and was higher in schoolchildren than in preschoolers (6.8 vs. 3.8 mm; *p< 0.01* ).**



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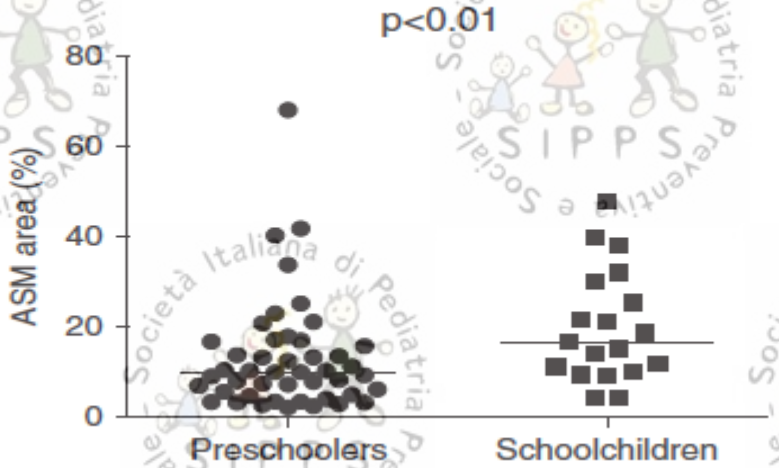
- ✓ 21 schoolchildren with severe asthma (group 3, 5–11.2 yr).

**ASM area was lower in preschoolers than in schoolchildren (9.8% vs. 16.5%; *p<0.01* ).**



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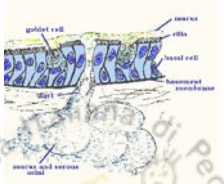
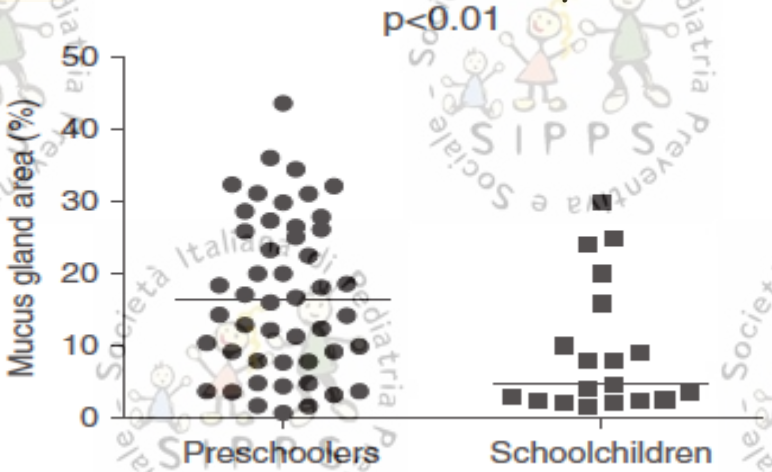


**Mucus gland area was higher in preschoolers than in schoolchildren (16.4% vs. 4.6%; *p<0.01* ).**



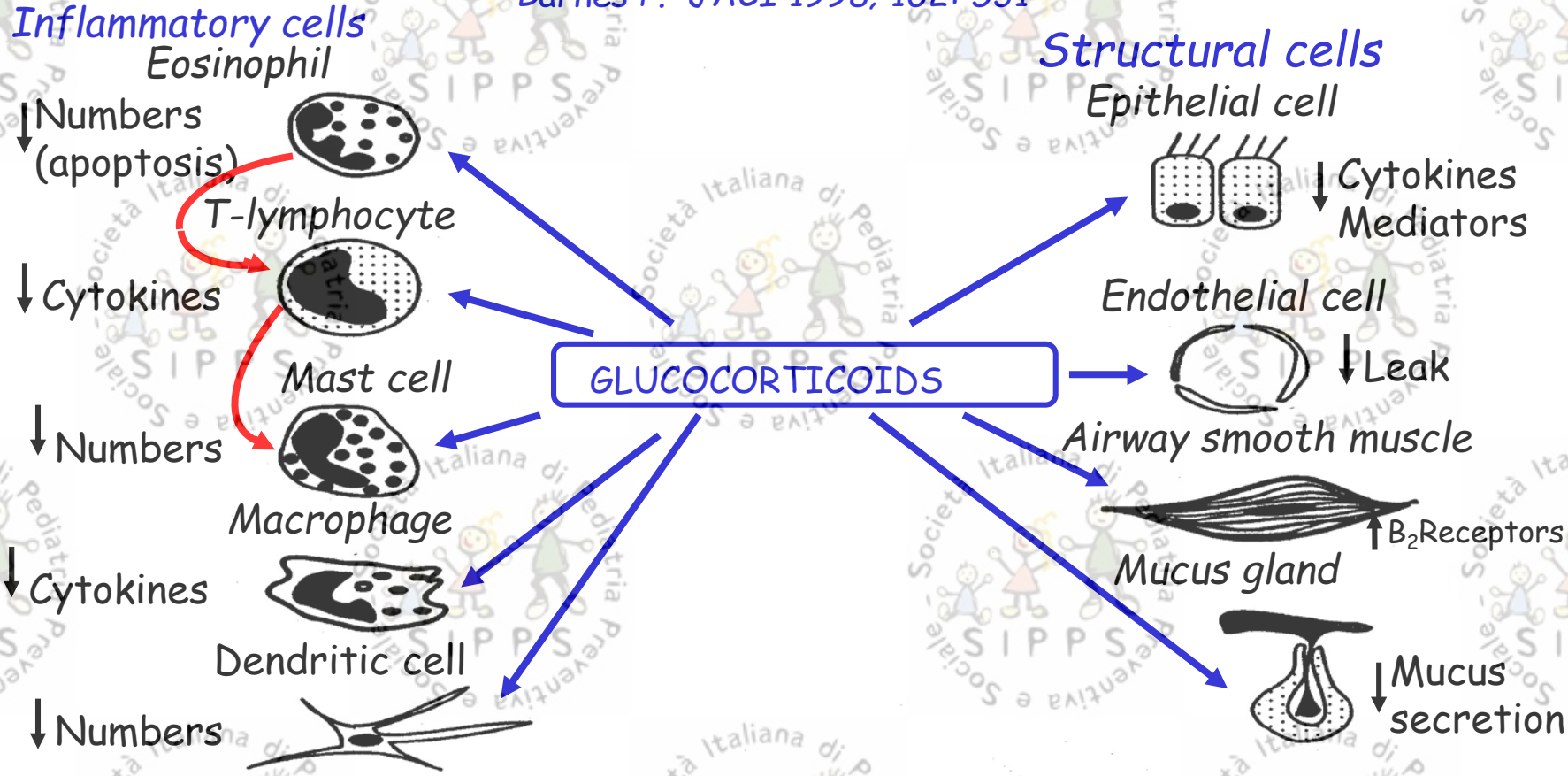
# Onset of Structural Airway Changes in Preschool Wheezers. A Window and Target for Secondary Asthma Prevention?

*Saglani S, AJRCCM 2015;192:121-133*

- The biopsy studies suggested a gradual development of airway remodeling in symptomatic children with severe wheezing between infancy and school age;
- The majority of structural airway changes in asthma develop early in life, in the first 5 years, in parallel with the abnormalities of lung function, and subsequently remain;
- In addition angiogenesis and epithelial shedding are increased compared with age-matched, nonwheezing controls.

Inhaled corticosteroids have effects on many inflammatory and structural cells that are involved in asthmatic inflammation.

*Barnes P. JACI 1998; 102: 531*



nature medicine

# Asthma phenotypes: the evolution from clinical to molecular approaches

**Table 1 Asthma phenotypes in relation to characteristics**

| | Natural history | Clinical and physiological features | Pathobiology and biomarkers | Genetics | Response to therapy |
|---|---|---|---|---|---|
| Early-onset allergic | Early onset; mild to severe | Allergic symptoms and other diseases | Specific IgE; $T_H2$ cytokines; thick SBM | 17q12; $T_H2$-related genes | Corticosteroid-responsive; $T_H2$-targeted |
| Late-onset eosinophilic | Adult onset; often severe | Sinusitis; less allergic | Corticosteroid-refractory eosinophilia; IL-5 | | Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory |
| Exercise-induced | | Mild; intermittent with exercise | Mast-cell activation; $T_H2$ cytokines; cysteinyl leukotrienes | | Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9 |
| Obesity-related | Adult onset | Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear | Lack of $T_H2$ biomarkers; oxidative stress | | Responsive to weight loss, antioxidants and possibly to hormonal therapy |
| Neutrophilic | | Low FEV1; more air trapping | Sputum neutrophilia; $T_H17$ pathways; IL-8 | | Possibly responsive to macrolide antibiotics |



Sally E Wenzel

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J ALLERGY CLIN IMMUNOL
■■■ 2018

# Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids

Michael C. Peters, MD,[a] Sheena Kerr, PhD,[a] Eleanor M. Dunican, MD,[a] Prescott G. Woodruff, MD,[a] Merritt L. Fajt, MD,[b] Bruce D. Levy, MD,[c] Elliot Israel, MD,[c] Brenda R. Phillips, MS,[d] David T. Mauger, PhD,[d] Suzy A. Comhair, PhD,[e] Serpil C. Erzurum, MD,[e] Mats W. Johansson, PhD,[f] Nizar N. Jarjour, MD,[g] Andrea M. Coverstone, MD,[h] Mario Castro, MD,[i] Annette T. Hastie, PhD,[j] Eugene R. Bleecker, MD,[j] Sally E. Wenzel, MD,[b] and John V. Fahy, MD,[a] for the National Heart, Lung and Blood Institute Severe Asthma Research Program 3

*San Francisco, Calif, Pittsburgh and Hershey, Pa, Boston, Mass, Cleveland, Ohio, Madison, Wis, St Louis, Mo, and Winston-Salem, NC*

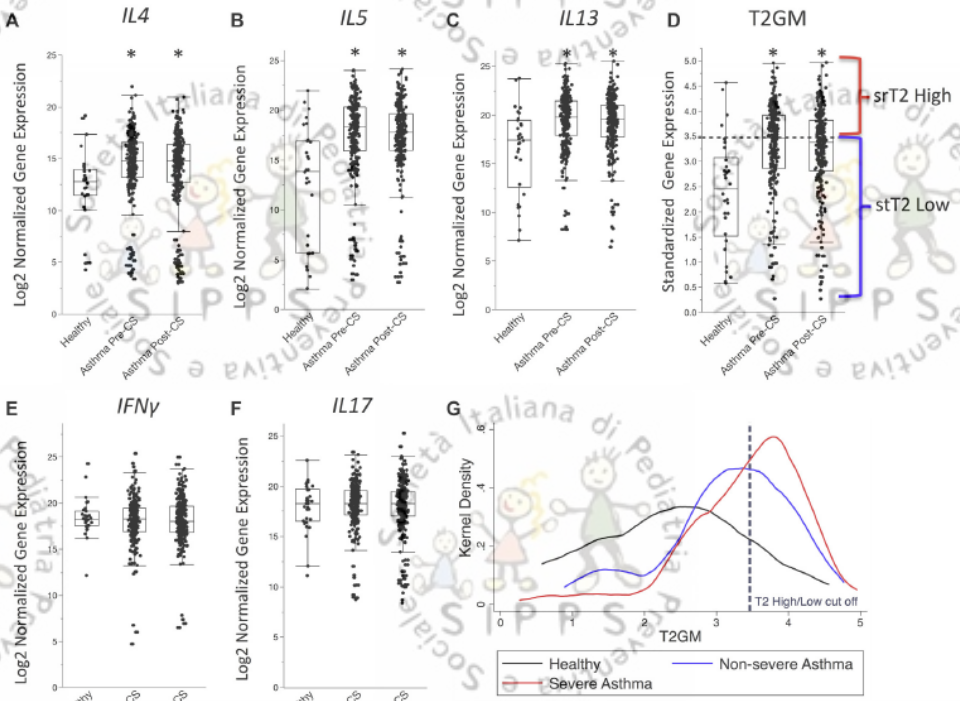
**Background:** Airway type 2 inflammation is usually corticosteroid sensitive, but the role of type 2 inflammation as a mechanism of asthma in patients receiving high-dose inhaled corticosteroids (ICSs) is uncertain.

**Objective:** We sought to determine whether airway type 2 inflammation persists in patients treated with ICSs and to evaluate the clinical features of patients with steroid-resistant airway type 2 inflammation.

**Methods:** We used quantitative PCR to generate a composite metric of type 2 cytokine gene expression (type 2 gene mean [T2GM]) in induced sputum cells from healthy control subjects, patients with severe asthma receiving ICSs (n = 174), and patients with nonsevere asthma receiving ICSs (n = 85). We explored relationships between asthma outcomes and T2GM values and the utility of noninvasive biomarkers of airway T2GM.

**Results:** Sputum cell T2GM values in asthmatic patients were significantly increased and remained high after treatment with intramuscular triamcinolone. We used the median T2GM value as a cutoff to classify steroid-treated type 2–low and steroid-resistant type 2–high (srT2-high) subgroups. Compared with patients with steroid-treated type 2–low asthma, those with srT2-high asthma were older and had more severe asthma. Blood eosinophil cell counts predicted srT2-high asthma when body mass index was less than 40 kg/m$^2$ but not when it was 40 kg/m$^2$ or greater, whereas blood IgE levels strongly predicted srT2-high asthma when age was less than 34 years but not when it was 34 years or greater.

# Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids




## Key messages

- ICSs or systemic corticosteroids do not fully suppress airway type 2 inflammation in a large subgroup of patients with severe asthma.
- Patients with steroid-resistant T2-high asthma are characterized by older age and more severe disease.
- Body weight and age modify the performance of blood-based biomarkers of airway type 2 inflammation.

J ALLERGY CLIN IMMUNOL

■■■ 2018

# Overweight/obesity status in preschool children associates with worse asthma but robust improvement on inhaled corticosteroids

J ALLERGY CLIN IMMUNOL
APRIL 2018

Jason E. Lang, MD, MPH,[a] Anne M. Fitzpatrick, PhD,[b] David T. Mauger, PhD,[c] Theresa W. Guilbert, MD,[e] Daniel J. Jackson, MD,[f] Robert F. Lemanske, Jr, MD,[g] Fernando D. Martinez, MD,[h] Robert C. Strunk, MD,[i†] Robert S. Zeiger, MD, PhD,[j] Wanda Phipatanakul, MD, MS,[l] Leonard B. Bacharier, MD,[i] Jacqueline A. Pongracic, MD,[m] Fernando Holguin, MD,[d] Michael D. Cabana, MD,[k] Ronina A. Covar, MD,[n] Hengameh H. Raissy, PharmD,[p] Monica Tang, MD,[a] and Stanley J. Szefler, MD, PhD,[o] for the National Institutes of Health/National Heart, Lung and Blood Institute AsthmaNet *Durham, NC; Atlanta, Ga; Hershey and Pittsburgh, Pa; Cincinnati, Ohio; Madison, Wis; Tuscon, Ariz; St Louis, Mo; San Diego and San Francisco, Calif; Boston, Mass; Chicago, Ill; Denver and Aurora, Colo; and Albuquerque, NM*

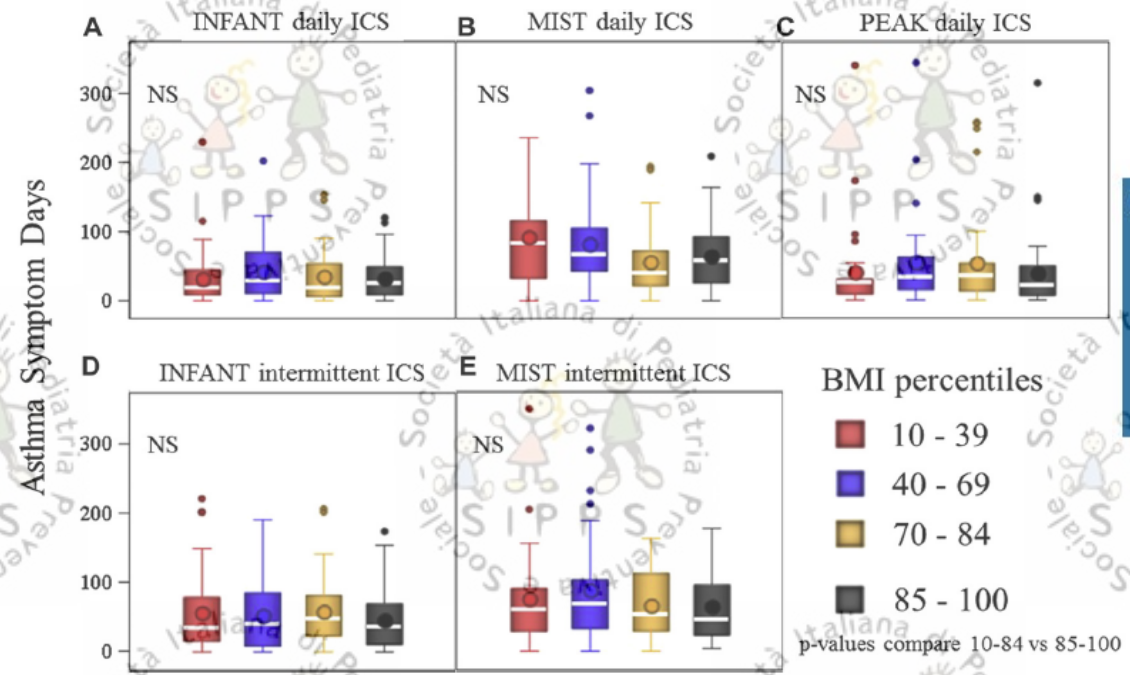
**Background:** Overweight/obesity (OW) is linked to worse asthma and poorer inhaled corticosteroid (ICS) response in older children and adults.

**Objective:** We sought to describe the relationships between OW and asthma severity and response to ICS in preschool children.

**Methods:** This *post hoc* study of 3 large multicenter trials involving 2- to 5-year-old children compared annualized asthma symptom days and exacerbations among normal weight (NW) (body mass index: 10th-84th percentiles) versus OW (body mass index: ≥85th percentile) participants. Participants had been randomized to daily ICS, intermittent ICS, or daily placebo. Simple and multivariable linear regression was used to compare body mass index groups.

**Results:** Within the group not treated with a daily controller, OW children had more asthma symptom days (90.7 vs 53.2, $P = .020$) and exacerbations (1.4 vs 0.8, $P = .009$) thanNW children did. Within the ICS-treated groups, OW and NW children had similar asthma symptom days (daily ICS: 47.2 vs 44.0 days, $P = .44$; short-term ICS: 61.8 vs 52.9 days, $P = .46$; as-needed ICS: 53.3 vs 47.3 days, $P = .53$), and similar

# Overweight/obesity status in preschool children associates with worse asthma but robust improvement on inhaled corticosteroids




**Key message**

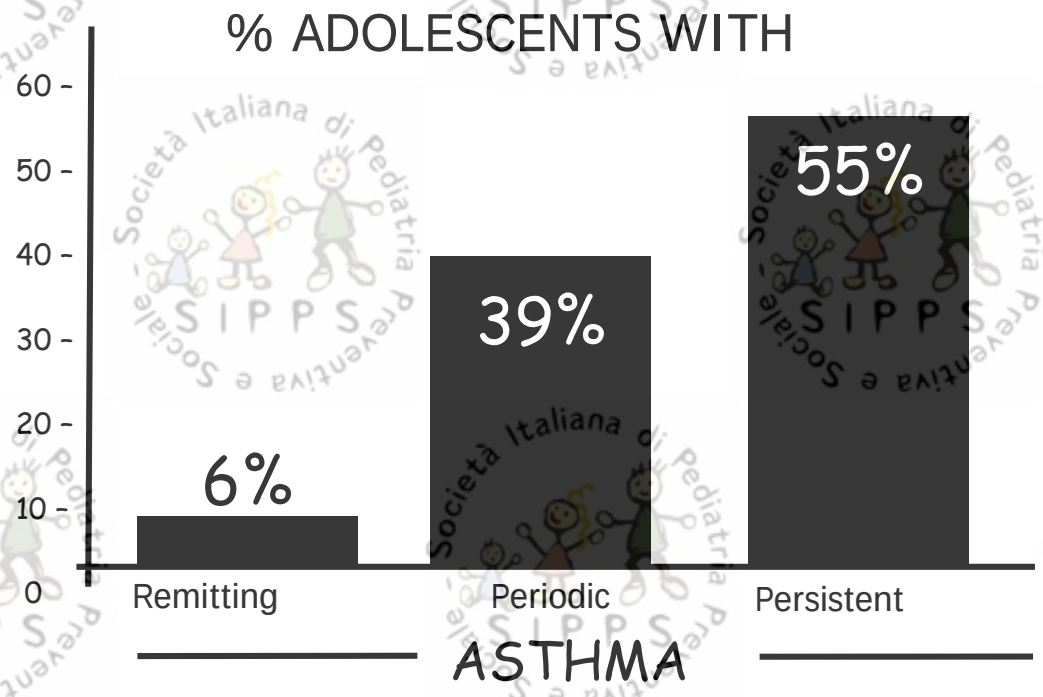
- OW status is a risk factor in preschoolers for greater asthma impairment and exacerbations.
- Unlike in older patients, OW in preschoolers is not associated with poor ICS response.

J ALLERGY CLIN IMMUNOL
APRIL 2018

# Predictors of remitting, periodic, and persistent childhood asthma

Ronina A. Covar, MD,[a] Robert Strunk, MD,[b] Robert S. Zeiger, MD, PhD,[c,d] Laura A. Wilson, ScM,[e] Andrew H. Liu, MD,[a] Scott Weiss, MD, MSc,[f] James Tonascia, PhD,[e] Joseph D. Spahn, MD,[a] and Stanley J. Szefler, MD,[a] for the Childhood Asthma Management Program Research Group *Denver, Colo, St Louis, Mo, San Diego, Calif, Baltimore, Md, and Boston, Mass*

- The Childhood Asthma Management Program (CAMP) in children with mild to moderate persistent asthma.
- 4.3 years treatment
- 4 years follow-up
- 909 participants.




JACI 2010

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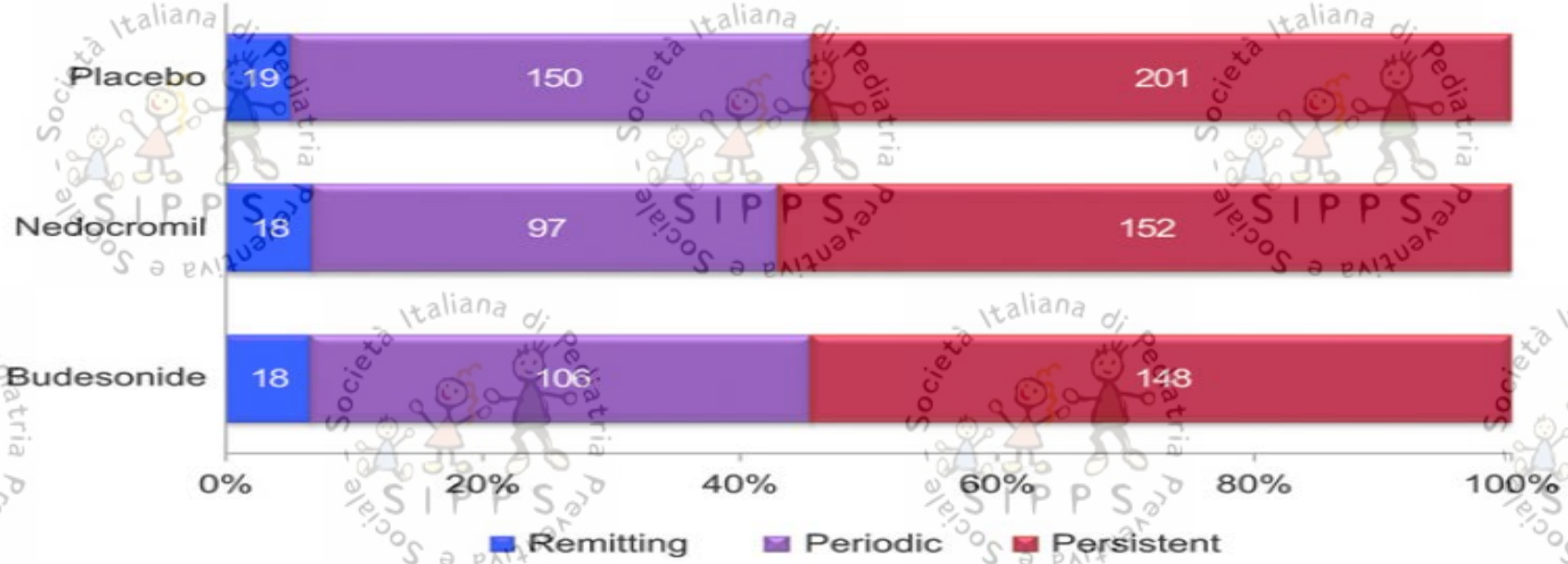
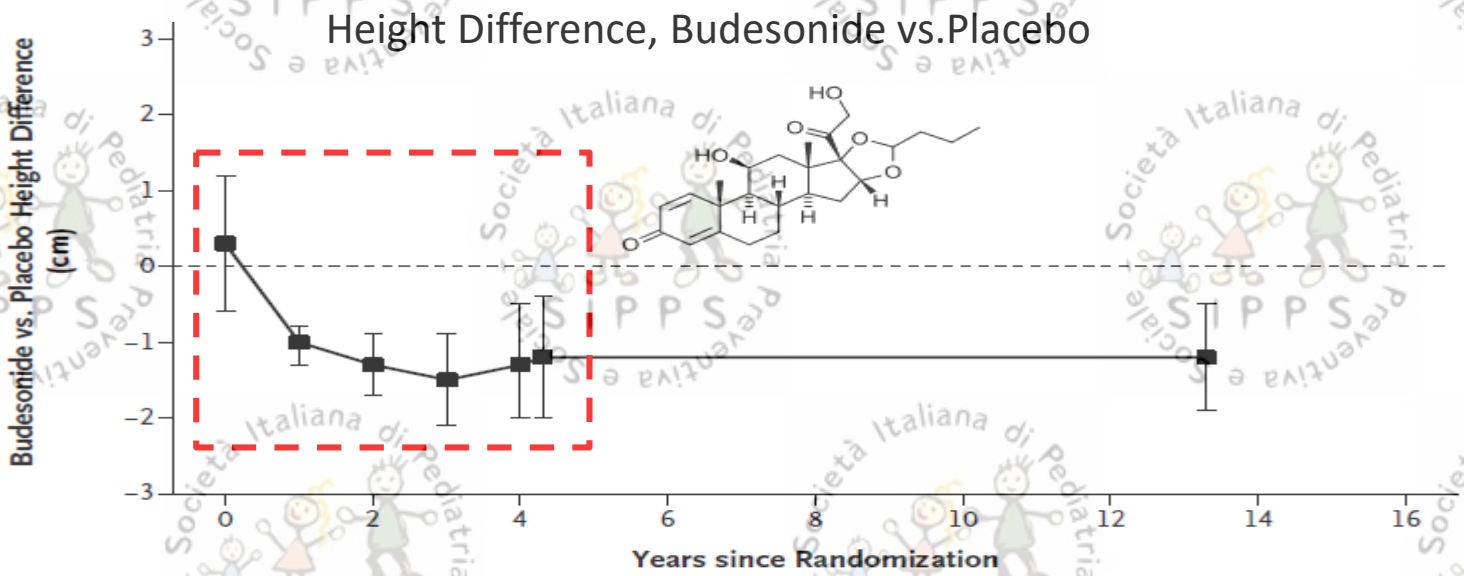



JACI 2010

# Effect of inhaled glucocorticoids in childhood on adult height in participants in the Childhood Asthma Management Program




| Mean Age (yr) | 9 | 11 | 13 | 25 |
|---|---|---|---|---|
| **No. of Participants** | | | | |
| Budesonide | 311 | 296 | 281 | 281 |
| Placebo | 418 | 396 | 383 | 377 |

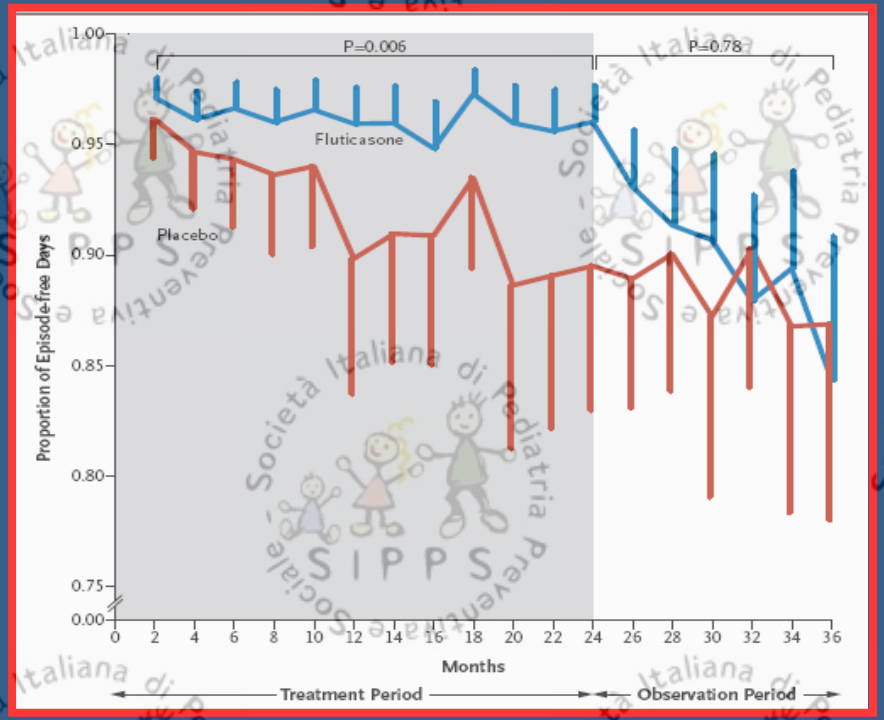
Kelly HW. N Engl J Med 2012, September 3

# LONG-TERM INHALED CORTICOSTEROIDS IN PRESCHOOL CHILDREN AT HIGH RISK FOR ASTHMA (PEAK Study)

*Guilbert NEJM 2006; 354: 1985*

- 285 bambini 2-3 a con (+) Indice Predittivo di Asma
- Fluticasone Prop. 100 µg x 2 o placebo per 2 anni
- 1 anno follow-up senza farmaci

**Proporzione bimensile di giorni liberi da sintomi durante il periodo di terapia di due anni ed il periodo di osservazione**



Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI

POSITION PAPER

# International consensus on (ICON) pediatric asthma

N. G. Papadopoulos[1], H. Arakawa[2], K.-H. Carlsen[3], A. Custovic[4], J. Gern[5], R. Lemanske[6], P. Le Souef[7], M. Mäkelä[8], G. Roberts[9], G. Wong[10], H. Zar[11], C. A. Akdis[12], L. B. Bacharier[13], E. Baraldi[14], H. P. van Bever[15], J. de Blic[16], A. Boner[17], W. Burks[18], T. B. Casale[19], J. A. Castro-Rodriguez[20], Y. Z. Chen[21], Y. M. El-Gamal[22], M. L. Everard[23], T. Frischer[24], M. Geller[25], J. Gereda[26], D. Y. Goh[27], T. W. Guilbert[28], G. Hedlin[29], P. W. Heymann[30], S. J. Hong[31], E. M. Hossny[32], J. L. Huang[33], D. J. Jackson[34], J. C. de Jongste[35], O. Kalayci[36], N. Aït-Khaled[37], S. Kling[38], P. Kuna[39], S. Lau[40], D. K. Ledford[41], S. I. Lee[42], A. H. Liu[43], R. F. Lockey[44], K. Lødrup-Carlsen[45], J. Lötvall[46], A. Morikawa[47], A. Nieto[48], H. Paramesh[49], R. Pawankar[50], P. Pohunek[51], J. Pongracic[52], D. Price[53], C. Robertson[54], N. Rosario[55], L. J. Rossenwasser[56], P. D. Sly[57], R. Stein[58], S. Stick[59], S. Szefler[60], L. M. Taussig[61], E. Valovirta[62], P. Vichyanond[63], D. Wallace[64], E. Weinberg[65], G. Wennergren[66], J. Wildhaber[67] & R. S. Zeiger[68]

**Keywords**
asthma; children; consensus; guidelines; wheeze.

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Edited by: Michael Wechsler

**Abstract**

Asthma is the most common chronic lower respiratory disease in childhood throughout the world. Several guidelines and/or consensus documents are available to support medical decisions on pediatric asthma. Although there is no doubt that the use of common systematic approaches for management can considerably improve outcomes, dissemination and implementation of these are still major challenges. Consequently, the International Collaboration in Asthma, Allergy and Immunology (iCAALL), recently formed by the EAACI, AAAAI, ACAAI, and WAO, has decided to propose an International Consensus on (ICON) Pediatric Asthma. The purpose of this document is to highlight the key messages that are common to many of the existing guidelines, while critically reviewing and commenting on any differences, thus providing a concise reference. The principles of pediatric asthma management are generally accepted. Overall, the treatment goal is disease control. To achieve this, patients and their parents should be educated to optimally manage the disease, in collaboration with healthcare professionals. Identification and avoidance of triggers is also of significant importance. Assessment and monitoring should be performed regularly to re-evaluate and fine-tune treatment. Pharmacotherapy is the cornerstone of treatment. The optimal use of medication can, in most cases, help patients control symptoms and reduce the risk for future morbidity. The management of exacerbations is a major consideration, independent of chronic treatment. There is a trend toward considering phenotype-specific treatment choices; however, this goal has not yet been achieved.

2012

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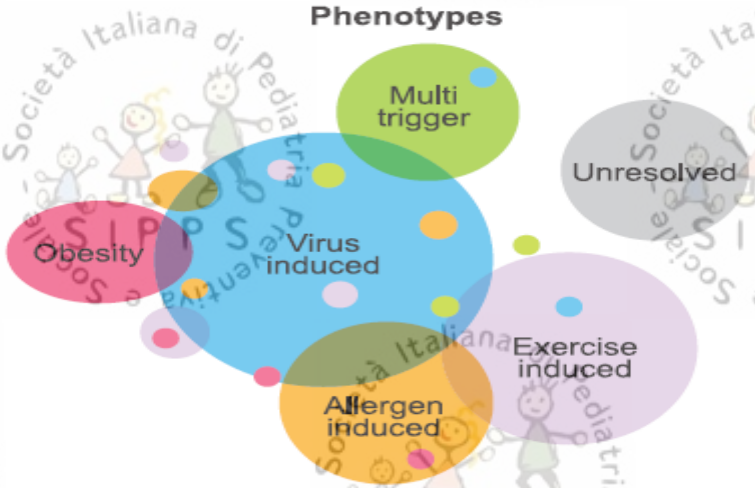
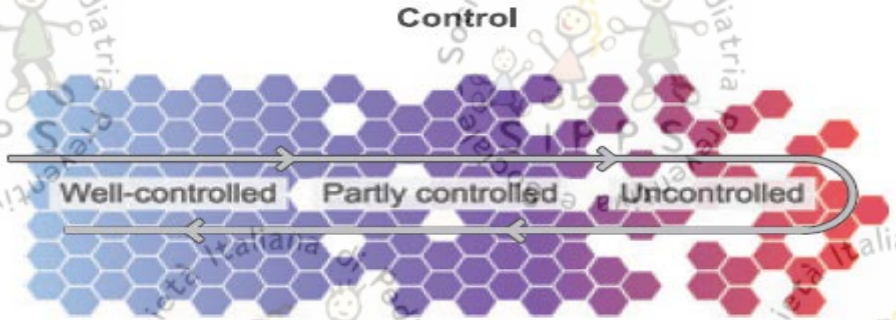
# International consensus on (ICON) pediatric asthma

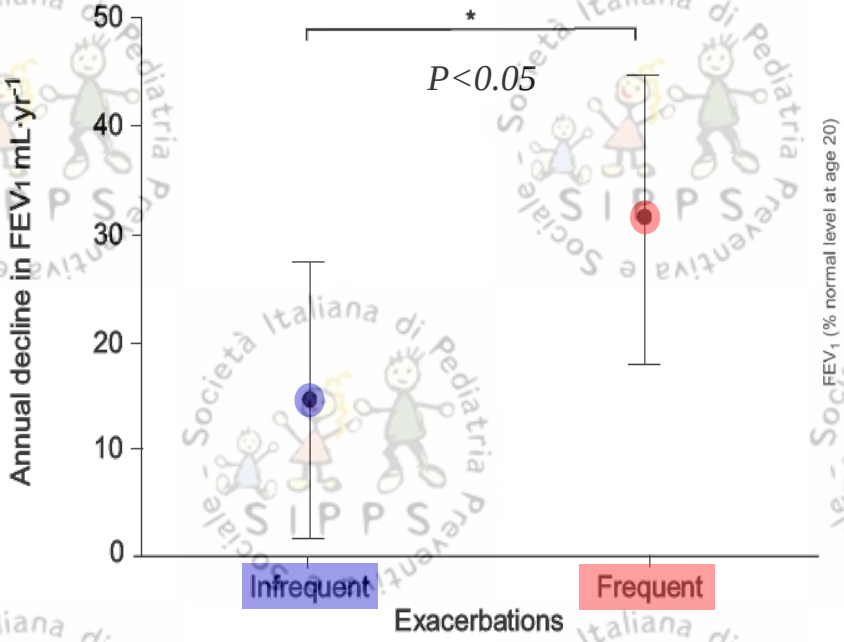


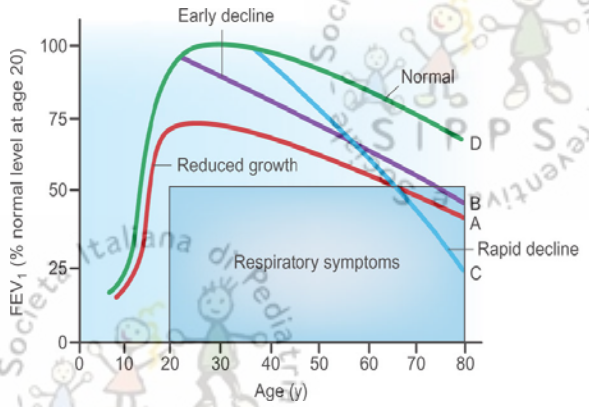




Papadopoulos et al. 2012

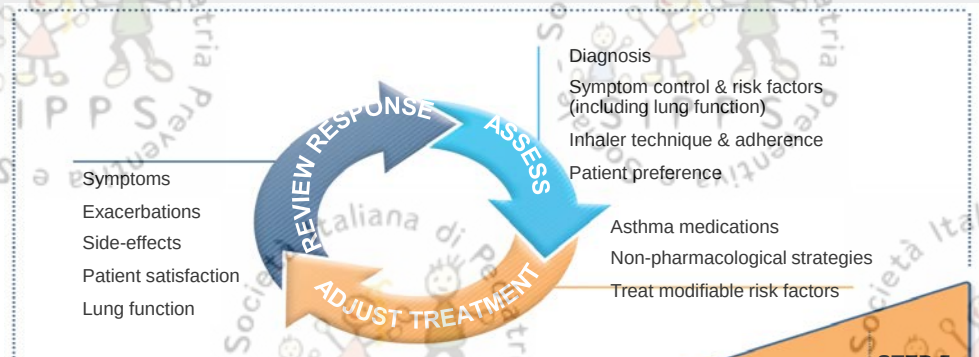
# Severe exacerbations predict excess lung function decline in asthma. *Bai TR, Eur Respir J. 2007;30:452*

**Estimated annual decline in $FEV_1$ in patients with infrequent or frequent asthma exacerbations**



# Stepwise approach to control asthma symptoms and reduce risk




| | STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|---|---|
| **PREFERRED CONTROLLER CHOICE** | | Low dose ICS | Low dose ICS/LABA** | Med/high ICS/LABA | Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5/5R* |
| Other controller options | *Consider low dose ICS* | *Leukotriene receptor antagonists (LTRA) Low dose theophylline** | *Med/high dose ICS Low dose ICS + LTRA (or + theoph*)* | *Add tiotropium*† Med/high dose ICS + LTRA (or + theoph*)* | *Add low dose OCS* |
| **RELIEVER** | As-needed short-acting beta$_2$-agonist (SABA) | | As-needed SABA or low dose ICS/formoterol# | | |

**REMEMBER TO...**

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- 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 FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Stopping ICS is not advised.

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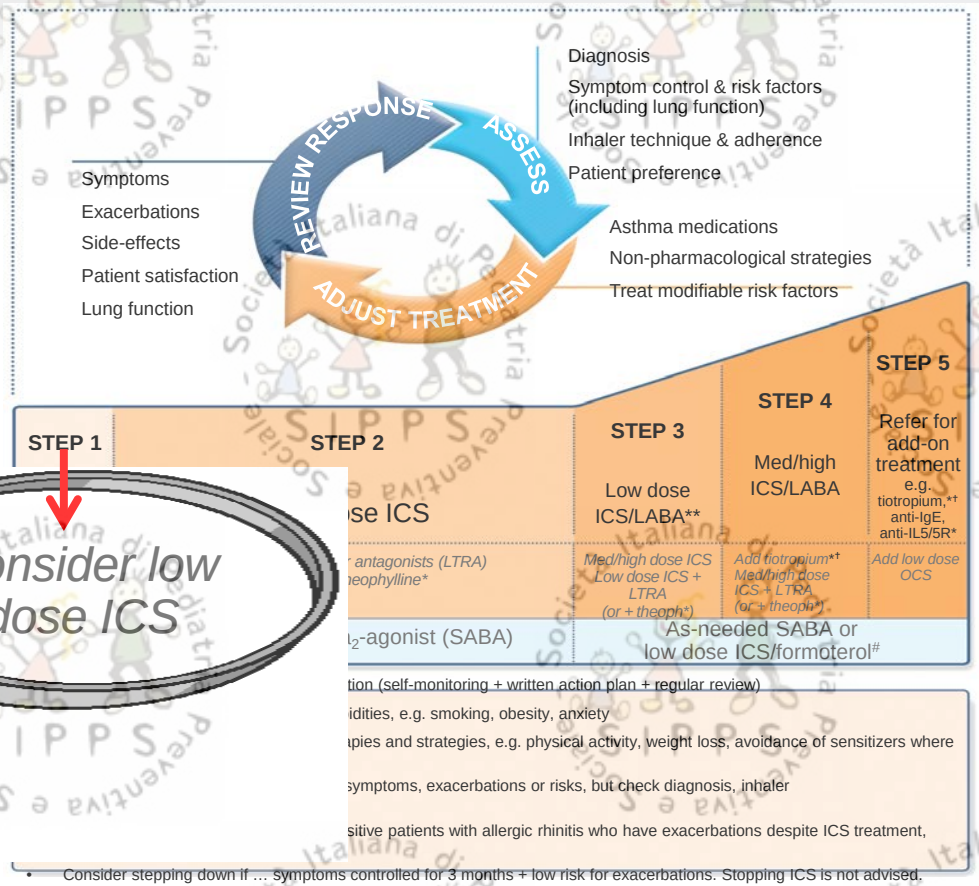
# Stepwise approach to control asthma symptoms and reduce risk



# Initial controller treatment for adults, adolescents and children 6–11 years

- Start controller treatment early
  - For best outcomes, initiate controller treatment as early as possible after making the diagnosis of asthma
- Indications for regular low-dose ICS - any of:
  - Asthma symptoms more than twice a month
  - Waking due to asthma more than once a month
  - Any asthma symptoms plus any risk factors for exacerbations
  - **i.e. most asthma patients, to reduce risk of flare-ups**
- Consider starting at a higher step if:
  - Troublesome asthma symptoms on most days
  - Waking from asthma once or more a week, especially if any risk factors for exacerbations
- If initial asthma presentation is with an exacerbation:
  - Give a short course of oral steroids and start regular controller treatment (e.g. high dose ICS or medium dose ICS/LABA, then step down)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Ann Allergy Asthma Immunol ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

# Impact of dosage timing of once-daily inhaled corticosteroids in asthma: A systematic review and meta-analysis

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ABSTRACT

**Background:** Once-daily inhaled corticosteroids (ICSs) are widely used as first-line therapy in patients with asthma.

**Objective:** To compare the efficacy of ICSs administered once daily in the morning or evening as determined by lung function.

**Methods:** Medline, Embase, and the Cochrane Central Register were searched for relevant clinical trials. The primary outcome was lung function assessed as trough forced expiratory volume in 1 second and peak expiratory flow at end point.

**Results:** Eight randomized clinical trials involving 1,234 patients were analyzed. The total number of patients treated with once-daily ICS in the morning and evening was 628 and 606, respectively. Pooled estimates showed that ICS administered once daily in the evening resulted in mild improvements in trough forced expiratory volume in 1 second (mean difference 0.05 L; 95% confidence interval 0.01–0.09; $P = .026$; $I^2 = 22.5\%$) and morning peak expiratory flow (mean difference 13.92 L/min; 95% confidence interval 5.77–22.06; $P = .001$; $I^2 = 13\%$) at end point compared with morning dosing. The change in use of rescue medicine and the incidence of adverse events with once-daily ICS were not significantly different between the 2 dosing times.

**Conclusion:** Compared with morning dosing, ICSs administered once daily in the evening seemed to provide some benefits in lung function for patients with asthma. However, because of methodologic limitations, further large-scale randomized clinical trials for dosing time of once-daily ICSs are needed.

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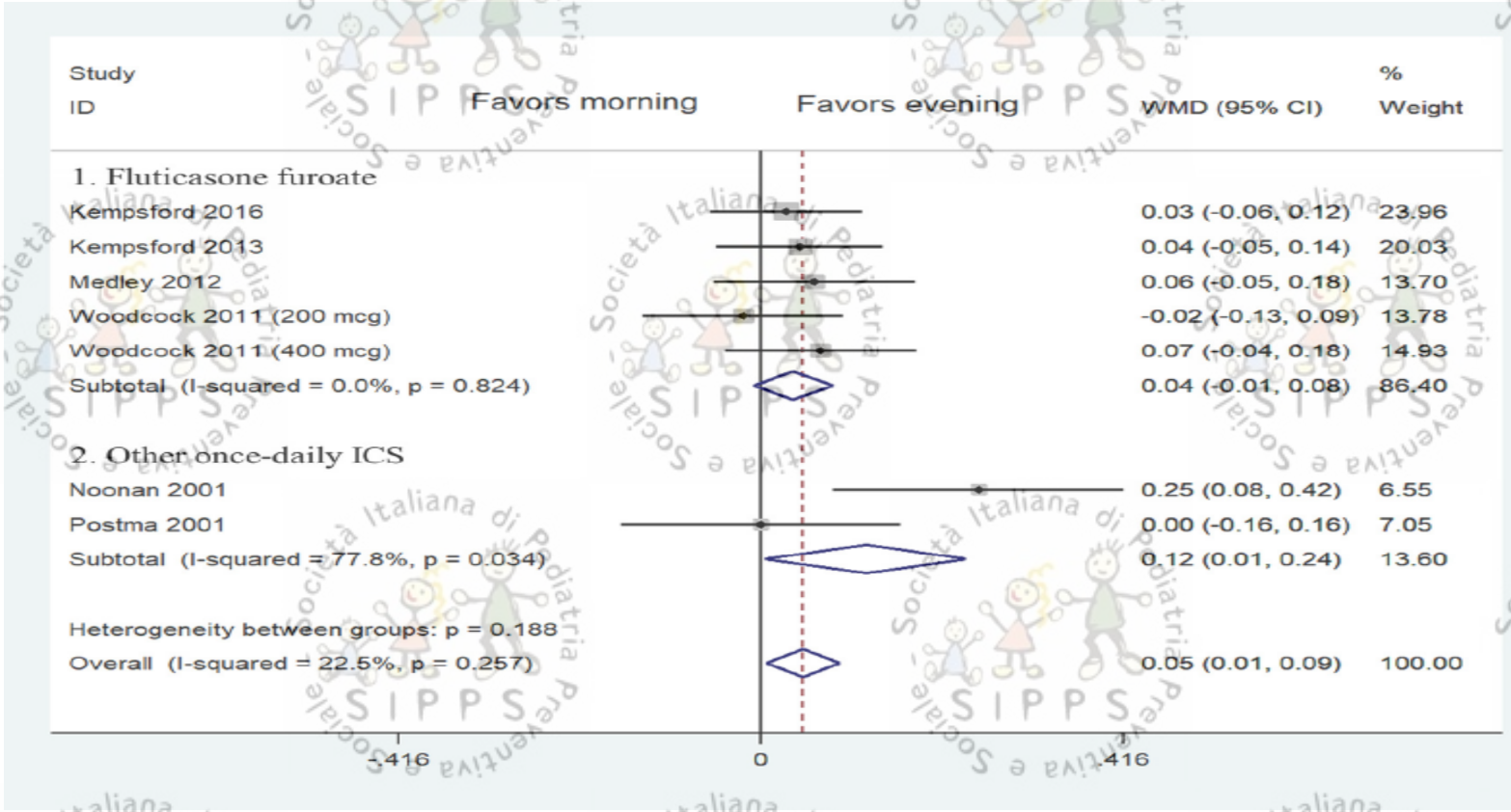
# Impact of dosage timing of once-daily inhaled corticosteroids in asthma: A systematic review and meta-analysis




J.-U. Song et al. / Ann Allergy Asthma Immunol ■■ (2018)

# Initial controller treatment for adults, adolescents and children 6–11 years

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  - For best outcomes, initiate controller treatment as early as possible after making the diagnosis of asthma
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  - Waking due to asthma more than once a month
  - Any asthma symptoms plus any risk factors for exacerbations
  - **i.e. most asthma patients, to reduce risk of flare-ups**
- Consider starting at a higher step if:
  - Troublesome asthma symptoms on most days
  - Waking from asthma once or more a week, especially if any risk factors for exacerbations
- If initial asthma presentation is with an exacerbation:
  - Give a short course of oral steroids and start regular controller treatment (e.g. high dose ICS or medium dose ICS/LABA, then step down)


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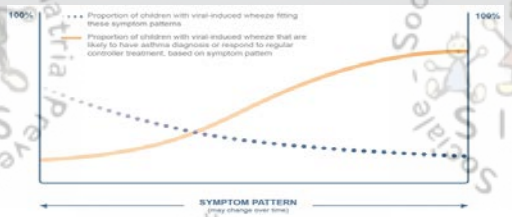
# Stepwise approach – pharmacotherapy (children ≤5 years)




| | STEP 1 | STEP 2 | STEP 3 | STEP 4 |
|---|---|---|---|---|
| **PREFERRED CONTROLLER CHOICE** | | **Daily low dose ICS** | **Double 'low dose' ICS** | Continue controller & refer for specialist assessment |
| *Other controller options* | | *Leukotriene receptor antagonist (LTRA)*<br>*Intermittent ICS* | *Low dose ICS + LTRA* | *Add LTRA*<br>*Inc. ICS frequency*<br>*Add intermitt ICS* |
| **RELIEVER** | As-needed short-acting beta$_2$-agonist (all children) | | | |
| **CONSIDER THIS STEP FOR CHILDREN WITH:** | Infrequent viral wheezing and no or few interval symptoms | Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year<br>Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks.<br>Give diagnostic trial for 3 months. | Asthma diagnosis, and not well-controlled on low dose ICS<br>First check diagnosis, inhaler skills, adherence, exposures | Not well-controlled on double ICS |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# Step 1 (children ≤5 years) – as-needed inhaled SABA

- Preferred option: as-needed inhaled SABA
  - Provide inhaled SABA to all children who experience wheezing episodes
  - Not effective in all children
- Other options
  - Oral bronchodilator therapy is not recommended (slower onset of action, more side-effects)
  - For children with intermittent viral-induced wheeze and no interval symptoms, if as-needed SABA is not sufficient, consider intermittent ICS. Because of the risk of side-effects, this should only be considered if the physician is confident that the treatment will be used appropriately.


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# Step 3 (children ≤5 years) – medium dose ICS + as-needed inhaled SABA

UPDATED 2018

- Indication
  - Asthma diagnosis, and symptoms not well-controlled on low dose ICS
  - First check symptoms are due to asthma, and check adherence, inhaler technique and environmental exposures
- Preferred option: medium dose ICS with as-needed inhaled SABA
  - Review response after 3 months
- Other options
  - Low-dose ICS + LTRA is another controller option
    - Blood eosinophils and atopy predict greater short-term response to moderate dose ICS than to LTRA *(Fitzpatrick JACI 2016)*
  - Relative cost of different treatment options in some countries may be relevant to controller choices


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# Rationale for recommendations about increasing controller therapy in asthma action plans

Many guidelines recommend treating worsening asthma with SABA alone until OCS are needed, but ...

- Most exacerbations are characterised by increased inflammation
- Most evidence for self-management involved doubling ICS dose
  - Outcomes were consistently better if the action plan prescribed both increased ICS, and OCS
- Lack of generalisability of placebo-controlled RCTs of doubling ICS
  - Participants were required to be highly adherent
  - Study inhalers were not started, on average, until symptoms and airflow limitation had been worsening for 4-5 days.
- Severe exacerbations are reduced by short-term treatment with
  - Quadrupled dose of ICS
  - Quadrupled dose of budesonide/formoterol
  - Early small increase in ICS/formoterol (maintenance & reliever regimen)
- Adherence by community patients is poor
  - Patients commonly take only 25-35% of prescribed controller dose
  - Patients often delay seeking care for fear of being given OCS


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# Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.

*Jackson DJ, N Engl J Med 2018;378:891*

**BACKGROUND:**

Asthma exacerbations occur frequently despite the regular use of asthma-controller therapies, such as inhaled glucocorticoids.

Clinicians commonly increase the doses of inhaled glucocorticoids at early signs of loss of asthma control.

However, data on the safety and efficacy of this strategy in children are limited.

2 X

4 X

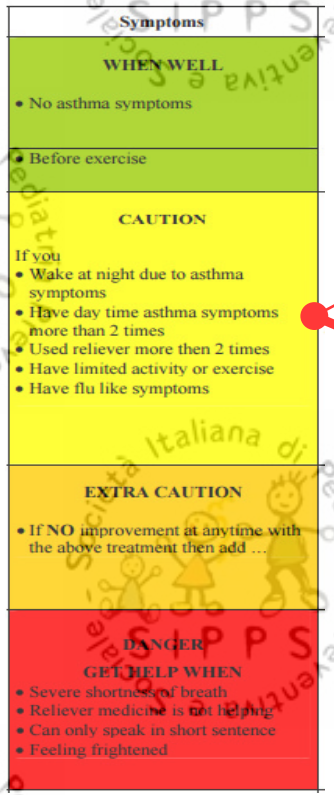
5 X

# Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.

*Jackson DJ, N Engl J Med 2018;378:891*

✓254 children, 5 to 11 years of age, who had mild-to-moderate persistent asthma and had had at least one asthma exacerbation treated with systemic glucocorticoids in the previous year.

✓Children were treated for 48 weeks with maintenance low-dose inhaled fluticasone propionate at a dose of 44 µg per inhalation, (2 inhalations twice daily) and were randomly assigned to either continue the same dose (low-dose group) or use a quintupled dose (high-dose group; fluticasone at a dose of 220 µg per inhalation, 2 inhalations twice daily) for 7 days at the early signs of loss of asthma control ("yellow zone").




FP 100 µg x 2

FP 100 µg x 2

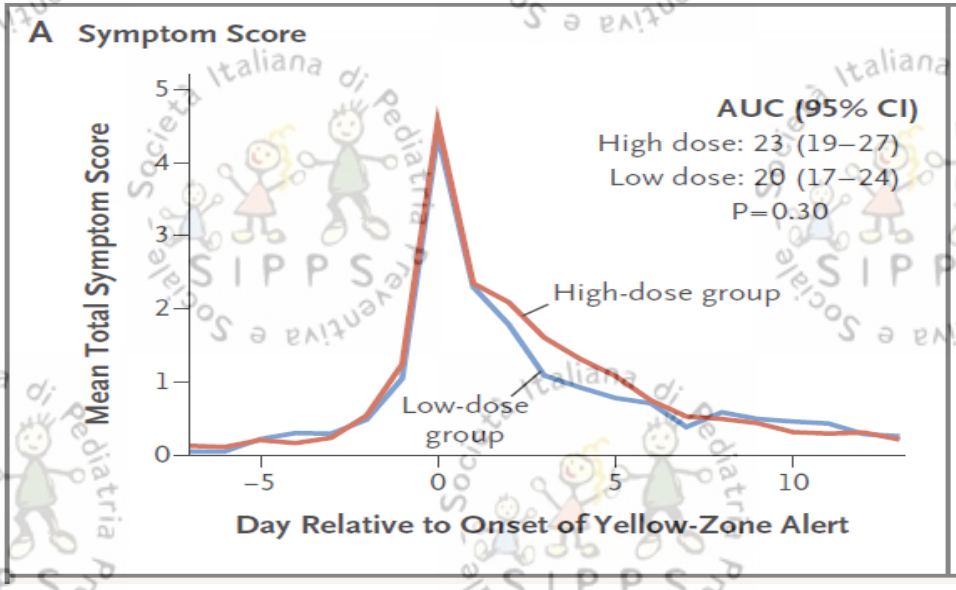
FP 500 µg x 2 for 7 days

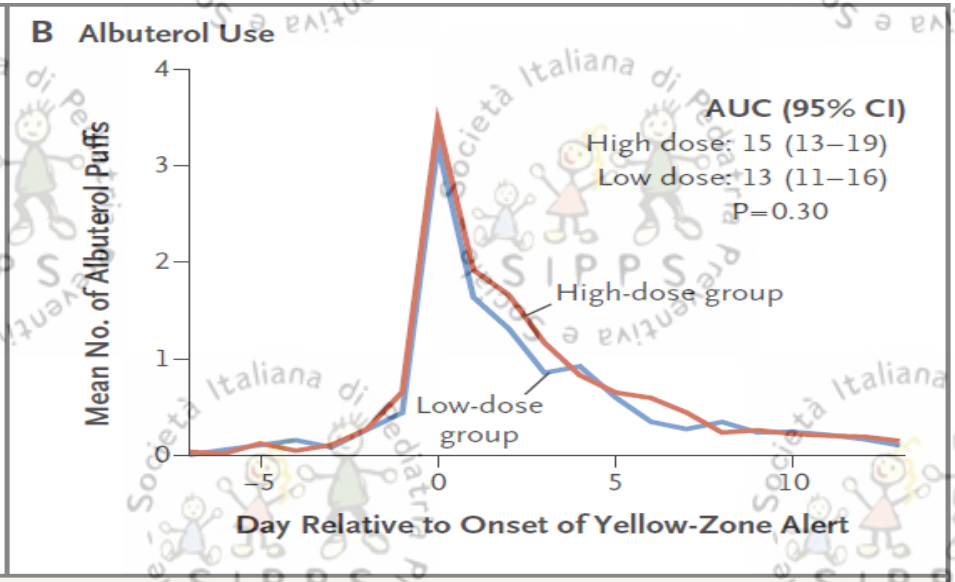
# Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.

*Jackson DJ, N Engl J Med 2018;378:891*

mean symptom scores 7 days before and 14 days after the onset of yellow-zone alerts

number of albuterol inhalations per day during the same time period




symptom scores, and albuterol use during yellow-zone episodes did not differ significantly between groups.

# Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.

*Jackson DJ, N Engl J Med 2018;378:891*

✓254 children, 5 to 11 years of age, who had mild-to-moderate persistent asthma and had had at least one asthma exacerbation treated with systemic glucocorticoids in the previous year.

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- The total glucocorticoid exposure was 16% higher in the high-dose group than in the low-dose group.

- The difference in linear growth between the high-dose group and the low-dose group was -0.23 cm per year *(P=0.06)*.

# Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.

*Jackson DJ, N Engl J Med 2018;378:891*

**In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth.**

- The total glucocorticoid exposure was 16% higher in the high-dose group than in the low-dose group.
- The difference in linear growth between the high-dose group and the low-dose group was -0.23 cm per year *(P=0.06)*.

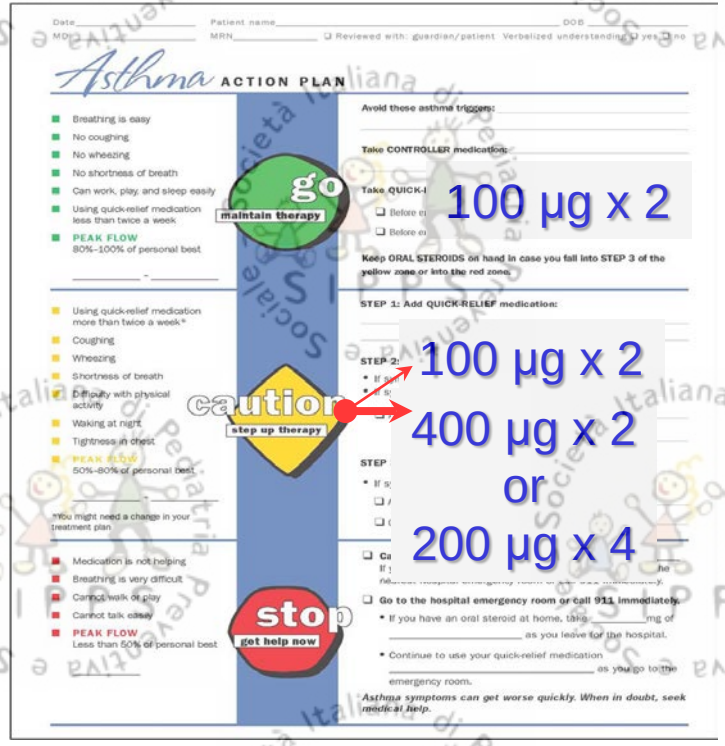
# Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations.

*McKeever T, N Engl J Med. 2018;378:902*

**BACKGROUND:**

Asthma exacerbations are frightening for patients and are occasionally fatal.

We tested the concept that a plan for patients to manage their asthma (self-management plan), which included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate, would reduce the incidence of severe asthma exacerbations among adults and adolescents with asthma.



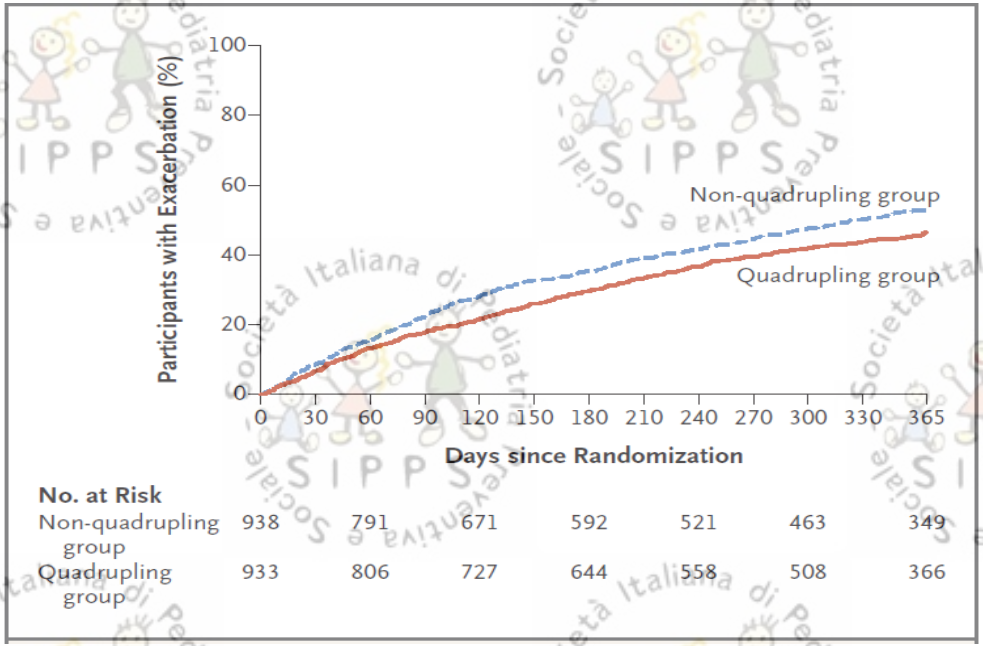
# Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations.

*McKeever T, N Engl J Med. 2018;378:902*

✓1871 adults and adolescents with asthma who were receiving inhaled glucocorticoids who had had at least one exacerbation in the previous 12 months

✓self-management plan that included an increase in the dose of inhaled glucocorticoids by a factor of 4 (quadrupling group) with the same plan without such an increase (non-quadrupling group), over a period of 12 months.

**The number of participants who had a severe asthma exacerbation in the year after randomization was 420 (45%) in the quadrupling group as compared with 484 (52%) in the non-quadrupling group,** with an adjusted hazard ratio for the time to a first severe exacerbation of 0.81 *(P=0.002)*.



# Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations.

*McKeever T, N Engl J Med. 2018;378:902*

- Approximately 50% of the patients included in the trial had an exacerbation, within a year, that led to treatment with oral glucocorticoids or an unscheduled health care consultation.

- We and others have, however, found that the previous recommendation to double the dose of inhaled glucocorticoids when asthma control is deteriorating was no more effective than not changing the dose.

- We observed a significant 19% reduction in the incidence of severe exacerbations, but the magnitude of reduction was smaller than expected.

# Escalating Inhaled Glucocorticoids to Prevent Asthma Exacerbations. *Editorial*

*Bardin PG. N Engl J Med. 2018;378:950.*

- Evidently, high doses of inhaled glucocorticoids do not prevent exacerbations, or may do so in only a small subgroup of patients.

- On the basis of causative factors alone, exacerbations are highly heterogeneous, and interactions between the underlying asthma phenotype and provoking factors are not understood.

- One solution could be to categorize asthma exacerbations by putative cause, such as infection, nonadherence to medication, and other exposures, and thus to “phenotype” asthma exacerbations.

# Conclusioni

**Good communication is essential** – establish a partnership with the patient

- Consider health literacy, personal goals and fears, and cultural issues

**Treatment choices**

- *Population-level decisions:* efficacy, effectiveness, safety, cost, regulations
- *Patient-level decisions for tailoring treatment:* also discuss patient characteristics (phenotype) that predict response or risk; patient preference; practical issues inhaler technique, adherence, and cost; treat modifiable risk factors; use non-pharmacological strategies where appropriate

**Stepwise medication adjustment**

- *Consider stepping up* if uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique, adherence and modifiable risk factors first
- *Consider stepping down* if symptoms controlled for 3 months and low risk for exacerbations. For adults, ceasing ICS is not advised.

**Written asthma action plan** for all patients

**The Global Initiative for Asthma (GINA) control-based cycle of asthma care.**
**This figure highlights key priorities in management of asthma in the GINA global asthma strategy.**

# Risk factors for asthma: is prevention possible?

*Richard Beasley, Alex Semprini, Edwin A Mitchell*

Asthma is one of the most common diseases in the world, resulting in a substantial burden of disease. Although rates of deaths due to asthma worldwide have reduced greatly over the past 25 years, no available therapeutic regimens can cure asthma, and the burden of asthma will continue to be driven by increasing prevalence. The reasons for the increase in asthma prevalence have not been defined, which limits the opportunities to develop targeted primary prevention measures. Although associations are reported between a wide range of risk factors and childhood asthma, substantiation of causality is inherently difficult from observational studies, and few risk factors have been assessed in primary prevention studies. Furthermore, none of the primary prevention intervention strategies that have undergone scrutiny in randomised controlled trials has provided sufficient evidence to lead to widespread implementation in clinical practice. A better understanding of the factors that cause asthma is urgently needed, and this knowledge could be used to develop public health and pharmacological primary prevention measures that are effective in reducing the prevalence of asthma worldwide. To achieve this it will be necessary to think outside the box, not only in terms of risk factors for the causation of asthma, but also the types of novel primary prevention strategies that are developed, and the research methods used to provide the evidence base for their implementation. In the interim, public health efforts should remain focused on measures with the potential to improve lung and general health, such as: reducing tobacco smoking and environmental tobacco smoke exposure; reducing indoor and outdoor air pollution and occupational exposures; reducing childhood obesity and encouraging a diet high in vegetables and fruit; improving feto-maternal health; encouraging breastfeeding; promoting childhood vaccinations; and reducing social inequalities.

*Lancet* 2015; 386: 1075–85

See Editorial page 1014

This is the first in a Series of two papers about Asthma

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GRAZIE PER
L'ATTENZIONE

# Thesis 2018

PERCORSI INTERATTIVI E FORMATIVI PEDIATRICI

14-15 Dicembre 2018

Hotel Royal Continental
Napoli