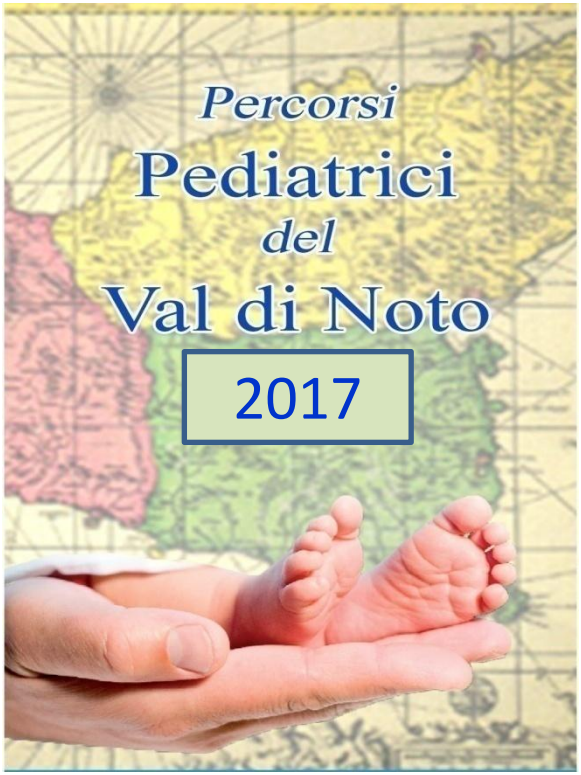


IL WHEEZING RICORRENTE: UN UNICO SUONO PER MOLTI STRUMENTI

SALVATORE LEONARDI
U.O.C DI BRONCOPNEUMOLOGIA PEDIATRICA

COMISO 10 FEBBRAIO 6017

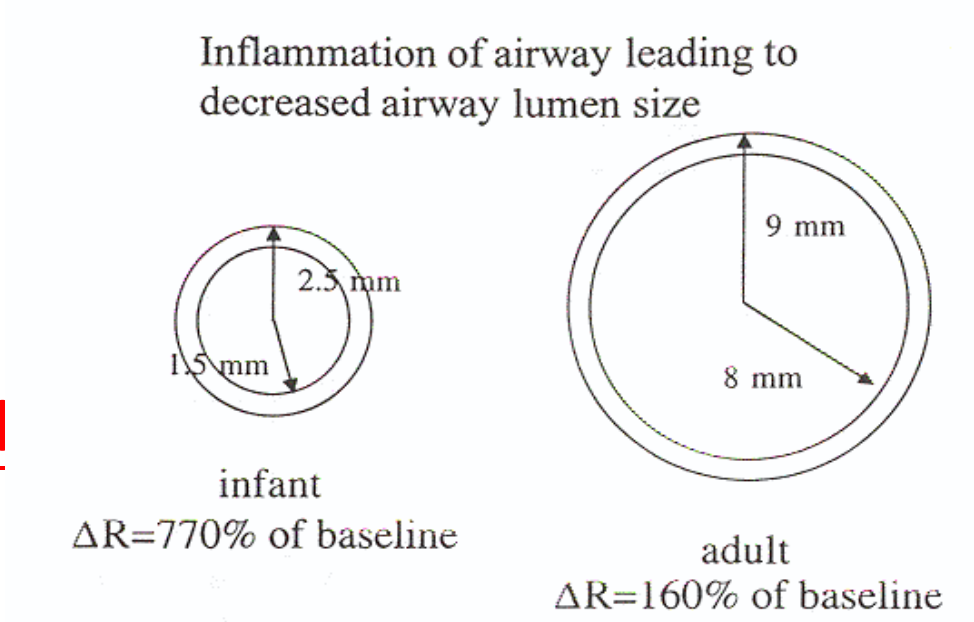
Wheezing disorders in preschool children

Wheezing illnesses are common and may affect as many as 50% of preschool children, resulting in substantial impact on the children, their families and the health care system

Martinez NEJM 1995

Qual' e' la causa dell'ostruzione delle vie

La maggior infanzia è dovuto al ema nelle vie aeree



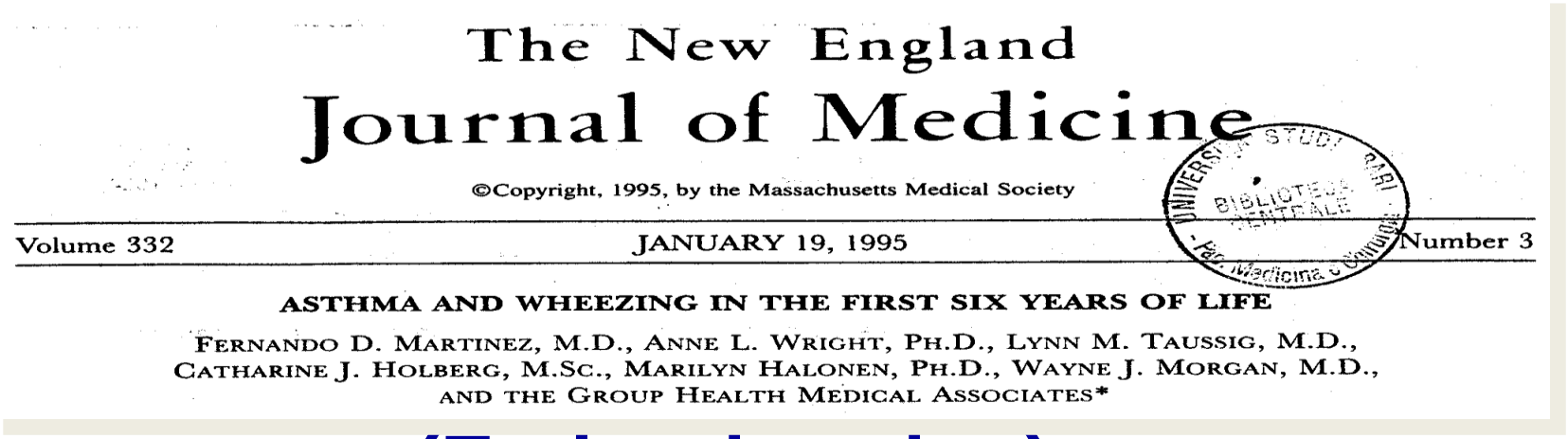
1 mm di edema nella trachea di un lattante comporta un incremento delle resistenze di 7,7 volte rispetto all'adulto

Wheezing

is a symptom/chest sound
and not a diagnosis !

Si intende per *Wheezing* il suono "*sibilante*", rilevabile soprattutto in fase di "*Espiro*", causato dal passaggio veloce e turbolento dell'aria attraverso un albero bronchiale più o meno ostruito

Col termine di *Wheezing Ricorrente (WR)* ci si riferisce abitualmente al paziente che, nei primi anni di vita, abbia presentato almeno 3-4 episodi di broncostruzione.



The New England
Journal of Medicine

Volume 332 JANUARY 19, 1995 Number 3

ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE

FERNANDO D. MARTINEZ, M.D., ANNE L. WRIGHT, PH.D., LYNN M. TAUSSIG, M.D.,
CATHARINE J. HOLBERG, M.SC., MARILYN HALONEN, PH.D., WAYNE J. MORGAN, M.D.,
AND THE GROUP HEALTH MEDICAL ASSOCIATES*

(Early wheezing)

Wheezing "transitorio"

Wheezing "persistente" (= early onset asthma)

.....not all early wheezing is asthma ...

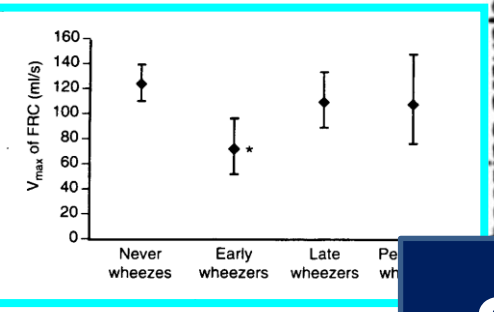
Nella maggior parte dei casi l'asma persistente esordisce entro i 2-3 aa

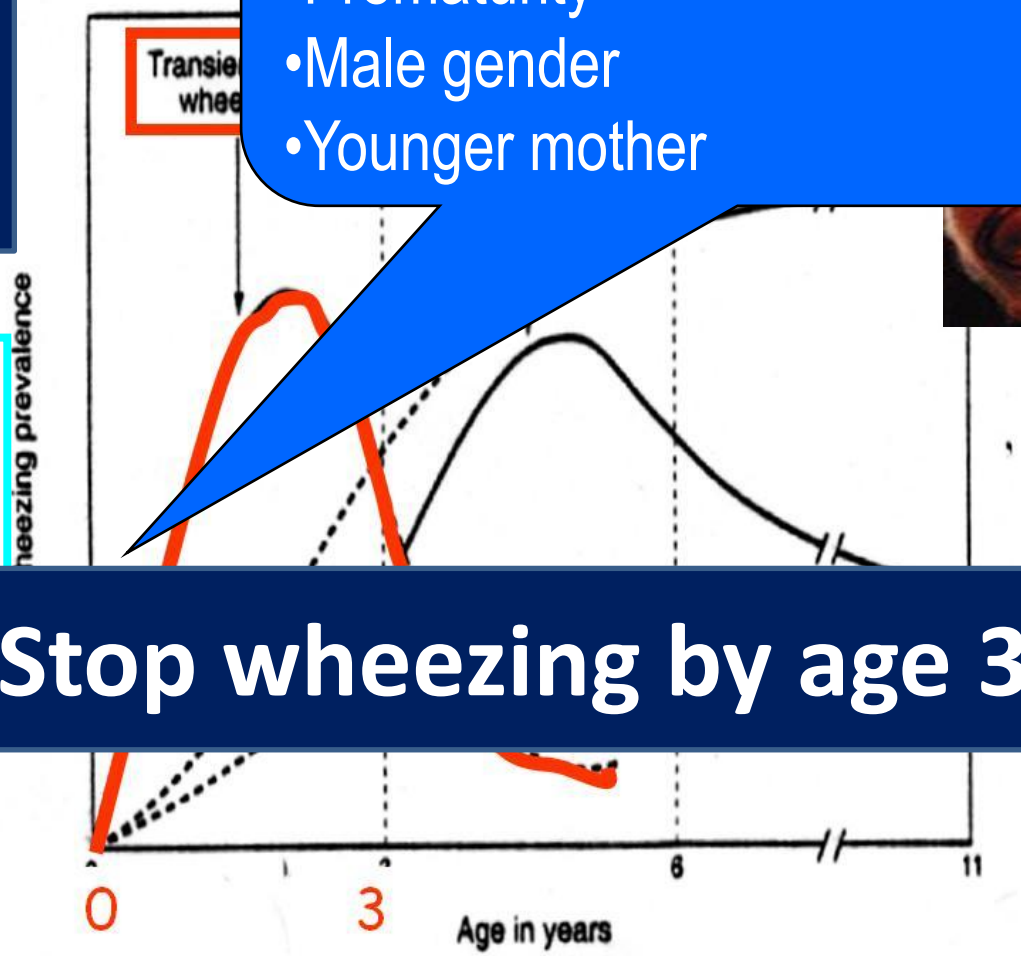
Solo il 40% degli "early wheezers" (<3 aa) continua ad avere wheezing a 6 aa ("persistent wheezers" = veri asmatici)

TRANSIENT EARLY WHEEZERS

- Reduced caliber of the airways at birth
- Passive smoking
- Prematurity
- Male gender
- Younger mother

Small airways



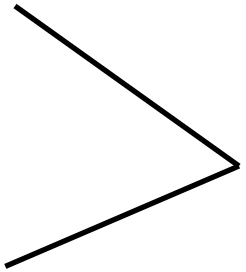


Stop wheezing by age 3 y

The Wheezing Infant and Child

Causes of **small airways obstruction**

- **Early onset Asthma**
- **GERD**
- **Bronchiolitis (viral)**
- **Cystic Fibrosis (1:3,000)**
- **Others:**
  - Bronchopulmonary Dysplasia (mixed Lg and Sm a/w)
  - Immunodeficiency (especially IgA -- 1:600)
  - Congenital Heart Disease with Pulm HTN or CHF/pulmonary edema (rare!)
  - Smoking (“Passive Smoking” - not rare, unfortunately!)
  - Primary Ciliary Dyskinesia (~1:16,000?)



“The Big 4”

The Wheezing Infant and Child

Causes of **Large Airways obstruction**

- **Endobronchial:**
  - Foreign body (all too common)
  - Tumor (carcinoid -- rare)
- **Intrinsic to wall**
  - Tracheomalacia (common)
  - Bronchomalacia (common)
  - Bronchial stenosis (rare)
- **Extrinsic Airway Compression**
  - Vascular ring/sling
  - Lymphadenopathy
  - Mediastinal mass (bronchogenic cyst)

Caso Clinico

- Shayla
- 8 mesi
- Nata alla 35^{esima}W da taglio cesareo d'urgenza per inizio di travaglio in pre-cesarizzata, dopo gravidanza decorsa fisiologicamente, col peso di 2340 g.

- La madre riferisce che la piccola presenta **tosse** persistente dai primi mesi di vita, **wheezing ricorrente** poco responsiva alle terapie prescritte dal pediatra curante, ed episodi frequenti di **rigurgito**.

FEBBRAIO 2016

Ricovero presso il reparto di Pediatria dell'Ospedale di [redacted] per **wheezing**.

RADIOGRAFIA DEL TORACE

rinforzo della trama ilo e perilare, seni costofrenici liberi, ombra cardio-timica nei limiti

ECOGRAFIA DELLA REGIONE GASTROESOFAGEA

breve passaggio di modesta quantità di contenuto gastrico in esofago

TERAPIA

claritromicina, betametasone, salbutamolo, aerosolica con ipertonica, antireflusso con alginato, senza beneficio clinico.

Ci viene trasferita per la persistenza della tosse e della sintomatologia bronco-ostruttiva

U.O. Broncopneumologia Pediatrica

E.O. ALL'INGRESSO

condizioni generali discrete, faringe iperemico,

rumori nasotrasmessi con incostanti ronchi.

LABORATORIO

lieve leucocitosi con monocitosi

TOSSE
WHEEZING

RIGURGITI

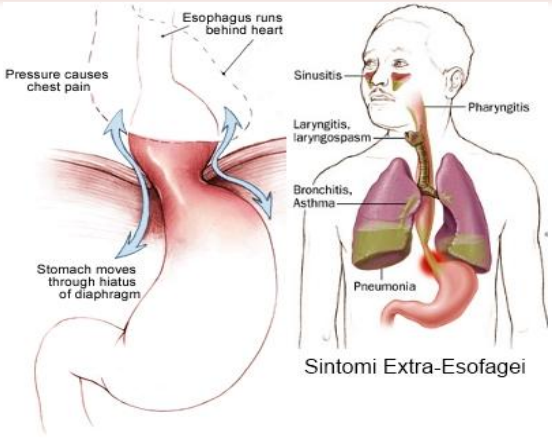
REFLUSSO GASTRO-ESOFAGEO?

Wheezing is a symptom/chest sound and not a diagnosis

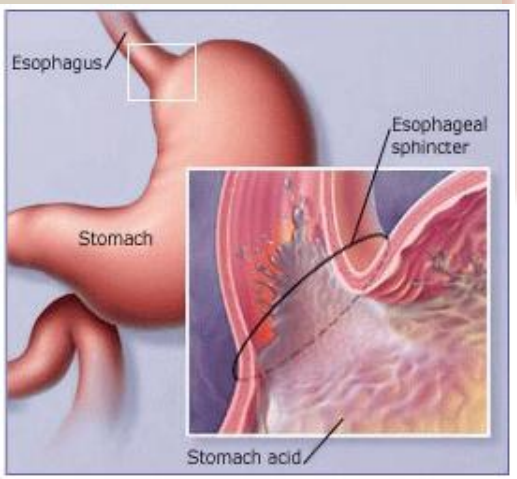
REFLUSSO GASTRO-ESOFAGEO

Sintomi Respiratori

- Alta prevalenza di RGE nell'asma e nelle polmoniti ricorrenti
- L'Asma puo' essere peggiorato dal RGE
- Tosse ricorrente , respiro difficoltoso, stridore
- Broncospasmo o wheezing
- Apnea, ALTE



Sintomi Extra-Esofagei



Acid and weakly acid gastroesophageal refluxes and type of respiratory symptoms in children

Michele Ghezzi [a], Michela Silvestri [a], Edoardo Guida [b], Angela Pistorio [c], Oliviero Sacco [a], Girolamo Mattioli [b], Vincenzo Jasonni [b], Giovanni A. Rossi [a,*]

[a] *Pediatric Pulmonology and Allergy Unit, G. Gaslini Institute, Largo G. Gaslini 5, 16147 Genoa, Italy*
[b] *Surgery Departments, G. Gaslini Institute, Genoa, Italy*
[c] *Clinical Epidemiology and Biostatistic Unit, G. Gaslini Institute, Genoa, Italy*

Table 1 Respiratory symptoms in the whole population and in each of the three age groups ($N = 112$).

	Whole population (No. 112), No. (%)	Infants (No. 26), No. (%)	Preschool-aged children (No. 33), No. (%)	School-aged children. (No. 53), No. (%)
Cough	89 (79.46)	18 (69.23)	27 (81.82)	44 (83.02)
Wheezy bronchitis and asthma	75 (66.96)	17 (65.38)	21 (63.64)	37 (69.81)
Recurrent lower respiratory tract infections	59 (52.68)	16 (61.54)	16 (48.48)	27 (50.94)
Apnoea/ALTE	13 (11.61)	7 (26.92)	3 (9.09)	3 (5.66)[a]
Laryngospasm	7 (6.25)	1 (3.85)	2 (6.06)	4 (7.55)

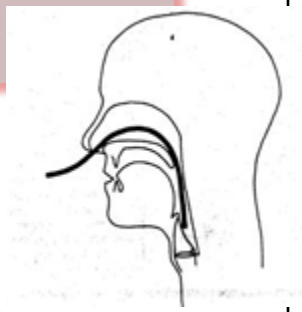
ALTE: apparent life-threatening event.
[a] $p = 0.036$ comparison between infants and school-aged children.

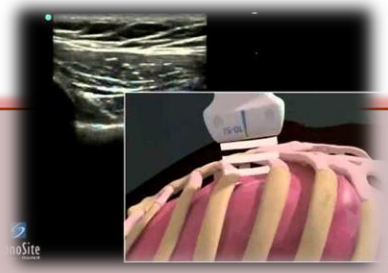
Respir Med 2011

Consulenza ORL

la laringoscopia mette in evidenza un'epiglottide adY nei piriformi profondi (come da laringomalacia), iperemia diffusa della mucosa laringea.

Si segnala altresì forte congestione della mucosa a livello della giunzione faringo-esofagea, aritenoidea ed inter-aritenoidea come da GERD.



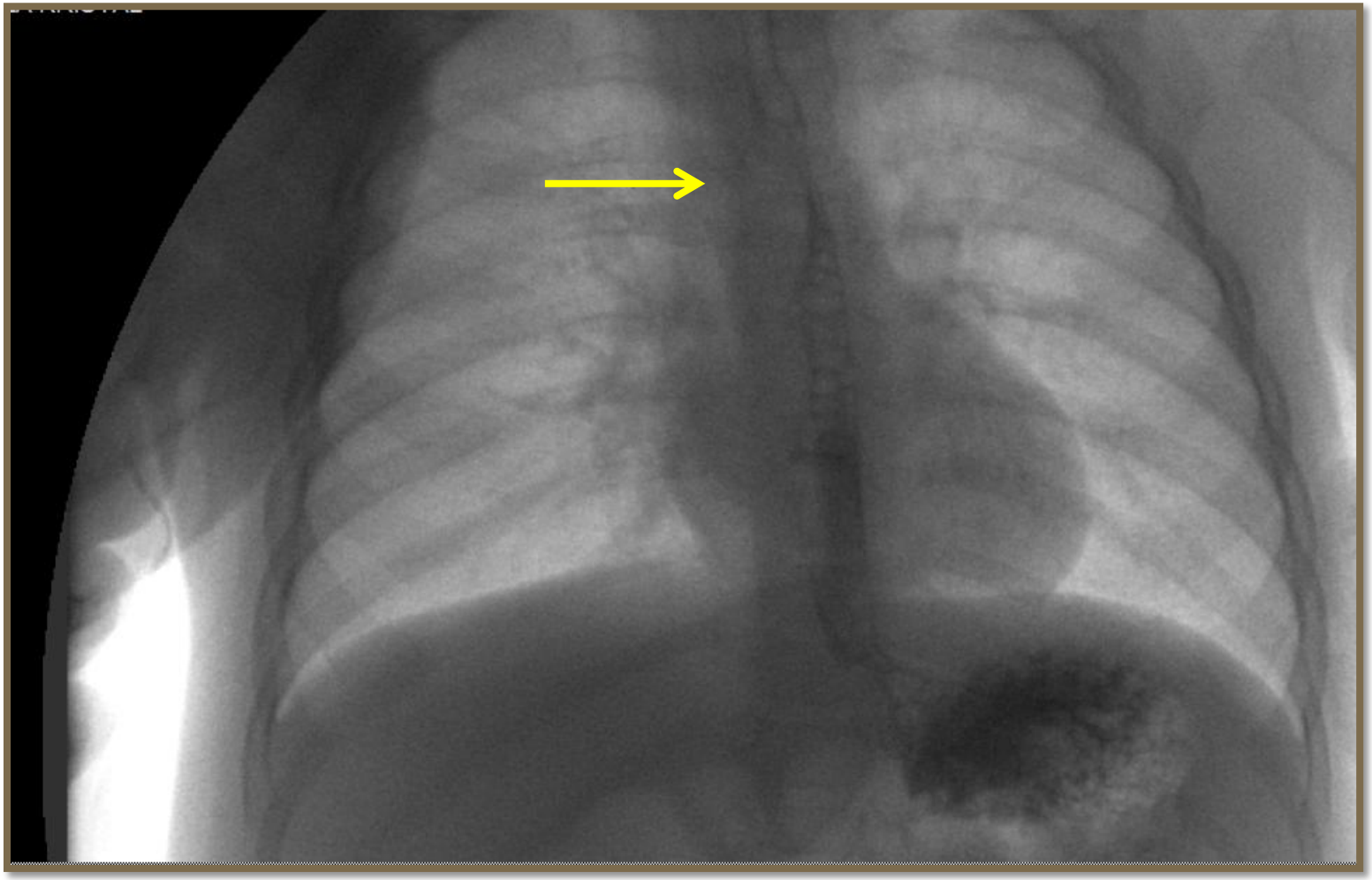


Ecografia torace

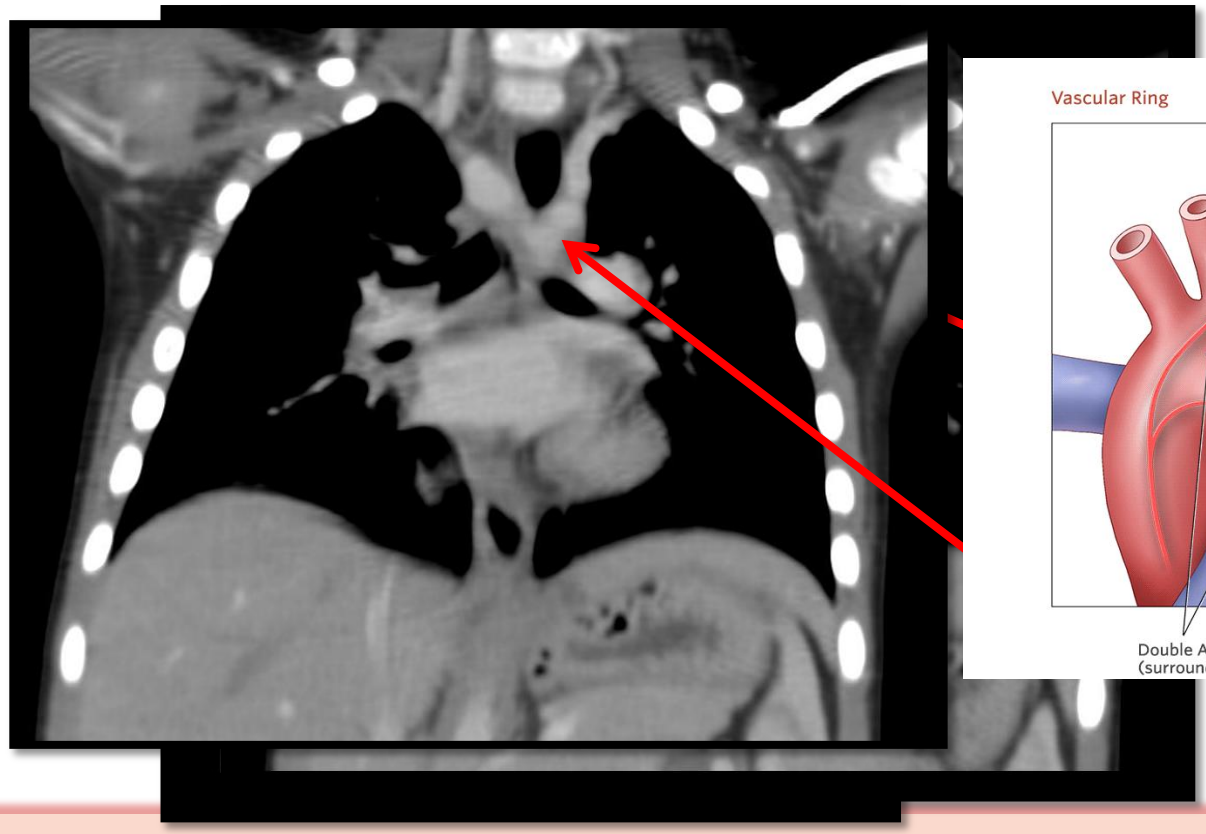
assenti versamenti pleurici. Assenti formazioni espansive o addensamenti periferici polmonari. Aditus mediastinico regolare, assenza di tumefazioni abnormi. Esofago craniale non dilatato.

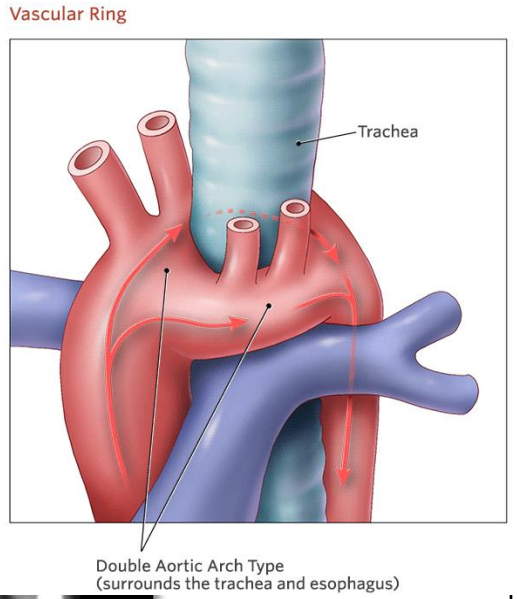
ESOFAGOGRAMMA

regolare il transito della colonna constrastografica attraverso l'esofago con una lieve irregolarità del profilo nel tratto medio in assenza di dilatazione del tratto a monte cervico-toracico, regolare il deflusso attraverso il cardias.



TCTORACE s/c mdc 08/04/2016





Presenza di **doppio arco aortico di tipo destro**. Non evidenza di corpi estranei endobronchiali apprezzabili con la metodica. Sembra apprezzarsi piccolo **diverticolo tracheale** in corrispondenza della parete postero-laterale destra. Sfumate aree di aumentata densità, con aspetto a ground glass, si apprezzano al LSD, da riferire verosimilmente ad aree disventilative.

“Early Wheezing”

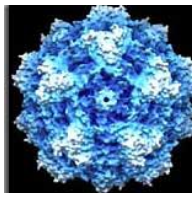
✓Come riconoscere nell’ambito
dell’ “early wheezing”
lo sviluppo di
un’ “early onset asthma”?

Viral wheeze

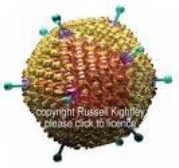
rhinovirus

RSV

influenzae

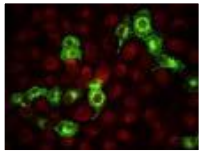


bocavirus



adenovirus

para-influenzae

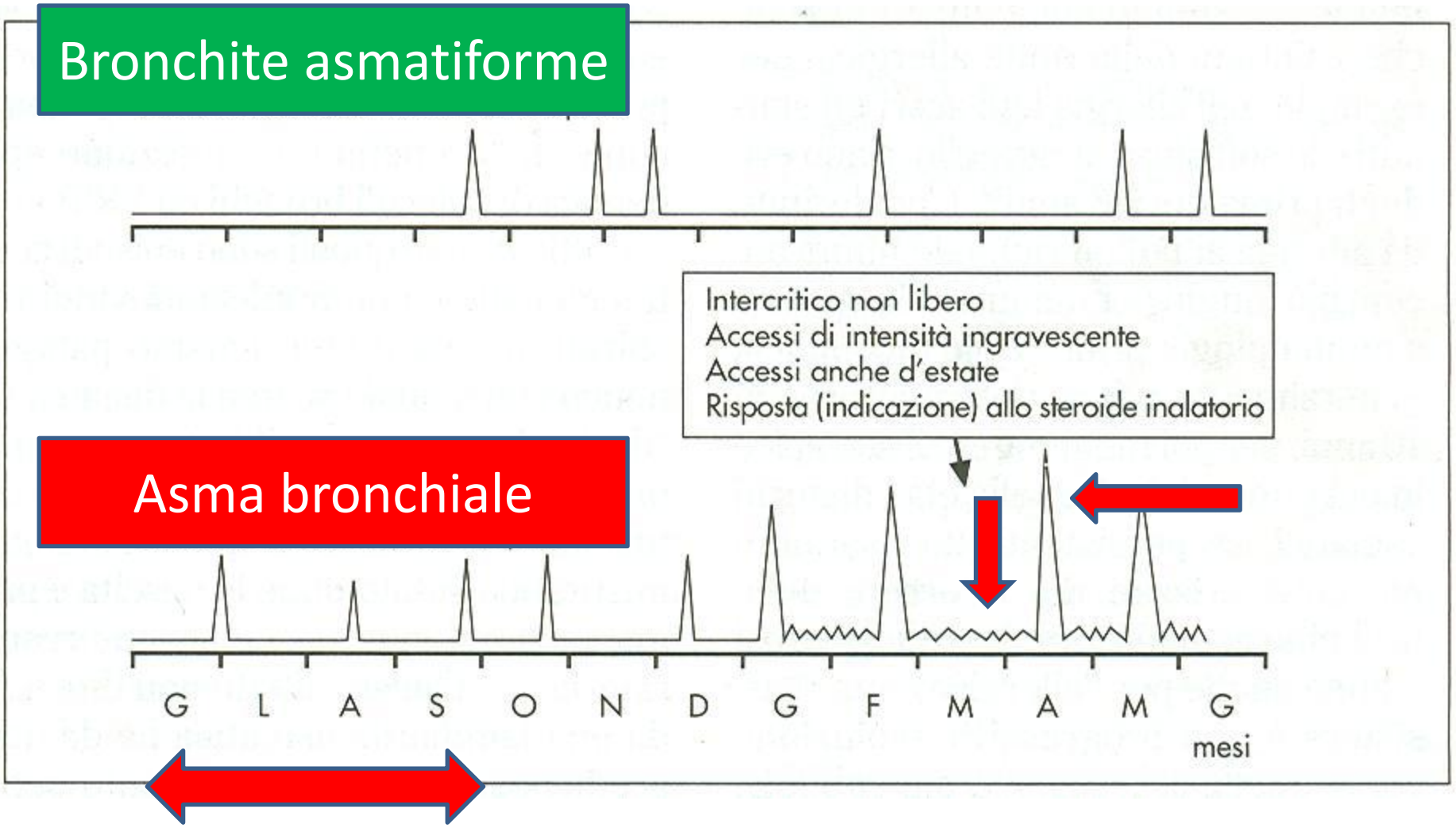


meta-pneumovirus

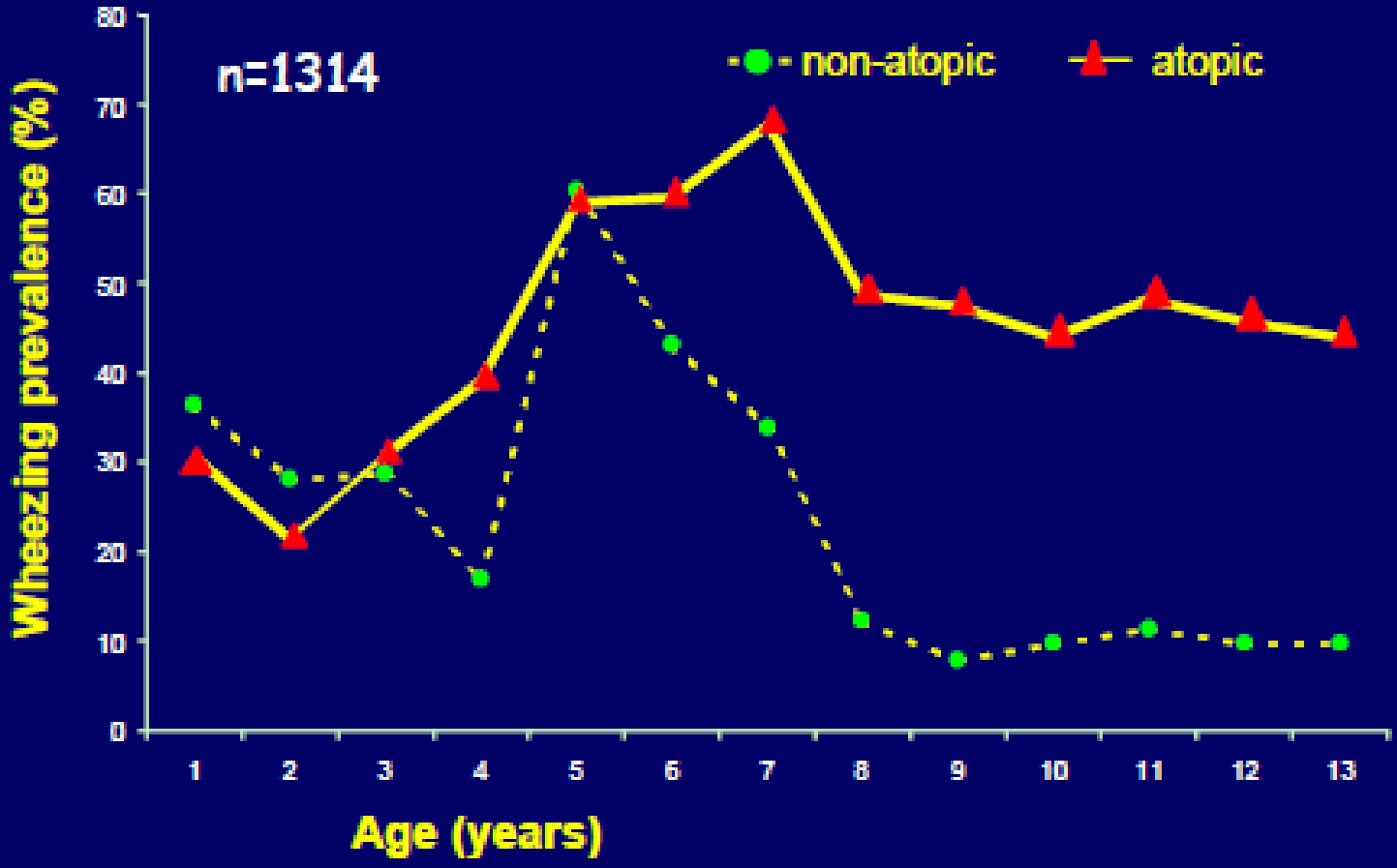
coronavirus

I TRIGGERS PIU' IMPORTANTI PER LE RIACUTIZZAZIONE DI ASMA E BRONCOSPASMO SONO LE INFEZIONI VIRALI

Ducharme NEJM 2009
Wald J Pediatr 1991


Bronchite asmatiforme
Intercritico non libero
Accessi di intensità ingravescente
Accessi anche d'estate
Risposta (indicazione) allo steroide inalatorio
Asma bronchiale
G L A S O N D G F M A M G
mesi

Atopic children (▲) are more likely to continue wheezing by the time they reach adolescence



MAS study – Illi et al Lancet 2006

Interrupter Resistance and Wheezing Phenotypes at 4 Years of Age

Jessica E. Brussee, Henriëtte A. Smit, Laurens P. Koopman, Alet H. Wijga, Marjan Kerkhof, Karen Corver, Ada P. H. Vos, Jorrit Gerritsen, Diederick E. Grobbee, Bert Brunekreef, Peter J. F. M. Merkus, and Johan C. de Jongste

Center for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven; Division of Respiratory Medicine, Department of Pediatrics, Sophia's Children's Hospital, Erasmus University Medical Center, Rotterdam; Department of Epidemiology and Statistics, University of Groningen, Groningen; Institute for Risk Assessment Sciences, Utrecht University, Utrecht; Department of Paediatric Respiratory Medicine, University Hospital Groningen, Groningen; and Julius Center for Health Sciences and Primary Care, Utrecht University Medical Center, Utrecht, The Netherlands

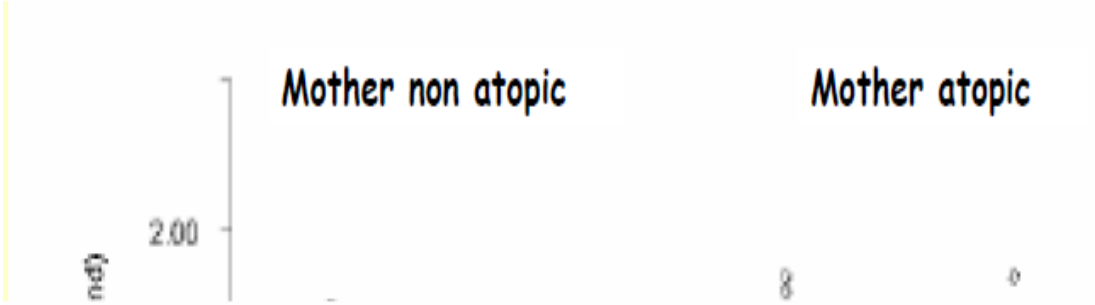


TABLE 2. MEAN INTERRUPTER RESISTANCE VALUES PER WHEEZING PHENOTYPE

Wheezing phenotype	Total Study Population			Nonatopic Mother			Atopic Mother		
	n	Mean (95% CI)*	z Score†	n	Mean (95% CI)*	z Score†	n	Mean (95% CI)*	z Score†
Never	482	0.95 (0.93, 0.97)	0.46	188	0.91 (0.88, 0.94)	0.31	294	0.98 (0.95, 1.01)‖	0.55
Early	236	0.95 (0.92, 0.98)	0.49	80	0.95 (0.90, 1.00)	0.49	156	0.96 (0.91, 1.00)	0.49
Late	22	0.96 (0.87, 1.05)	0.52	6	1.07 (0.85, 1.28)	0.89	16	0.92 (0.82, 1.02)	0.37
Persistent	98	1.08 (1.02, 1.14)‖,¶,#	0.96	29	1.10 (0.99, 1.21)‖,¶	1.04	69	1.07 (1.01, 1.14)‖,¶,#	0.92

Valuta la funzionalità respiratoria del bambino durante respiro a volume corrente

Misura il flusso aereo e la pressione alla bocca tramite un sistema di interruzione (valvola)

Criteri di Rischio per Asma nell'Early Wheezing

(Castro-Rodriguez, AJRCCM 2000;162:1403)

Criteri Maggiori

1. Asma nei genitori
2. Dermatite atopica

Criteri Minori

a

..piu' del 95 dei bambini con API negativo nei primi 3 anni di vita non sviluppa asma tra i 6 e i 13 anni

1 criterio

Wheezing precoce

ng precoce
requente

Asma nel 59%

Asma nel 76 %

Diagnosing asthma: the 3 R's

- **R**ecurrent
  - 3 or more episodes of wheezing or prolonged cough
- **R**eversible
  - With bronchodilator or corticosteroids
- **R**eactive
  - Pediatric asthma almost always has a trigger!

“Early Wheezing ed Asma ”

- ✓Quale terapia praticare?

La terapia del bambino con wheezing in eta' prescolare

Pre-school Wheeze: More Questions Than Answers

Monika Gappa, MD[1]* and Andrew Bush, MD[2]

Practice Imperfect — Treatment for Wheezing in Preschoolers

Andrew Bush, M.D.

The Challenge of Managing Wheezing in Infants

Urs Frey, M.D., Ph.D., and Erika von Mutius, M.D., M.Sc.

The NEW ENGLAND JOURNAL of MEDICINE

ovvero l'argomento dei MA.....

Asthma in the preschool child: Still a rose by any other name? Allan B. Becker,

WHEEZING DISORDERS IN PRESCHOOL CHILDREN

RECOMMENDATIONS:

DEFINITIONS OF PHENOTYPES (based on low-level evidence)

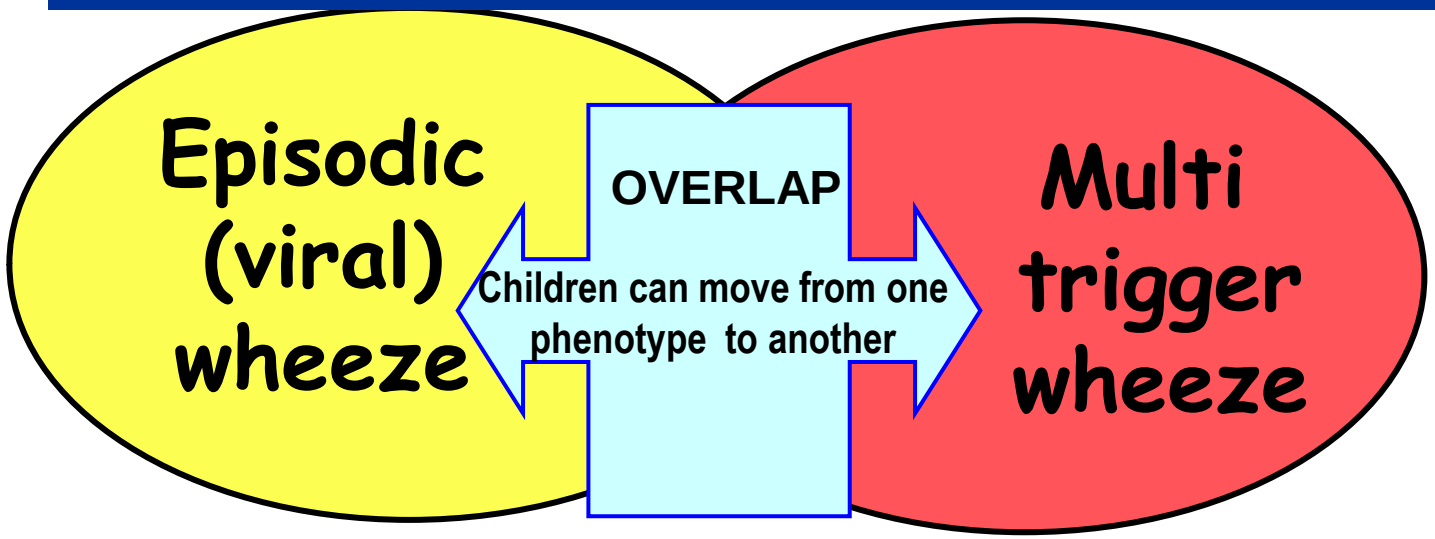
1) For clinical purposes, wheeze should be classified as episodic (viral) or multiple-trigger wheeze.

2) Use of the terms "transient", "persistent" wheeze should be limited to population-based cohort studies and should not be used clinically.

3) The term asthma should probably not be used in preschool children (lack of data regarding underlying inflammation).

Brand ERJ 2008

WHEEZING IN PRE-SCHOOL CHILDREN



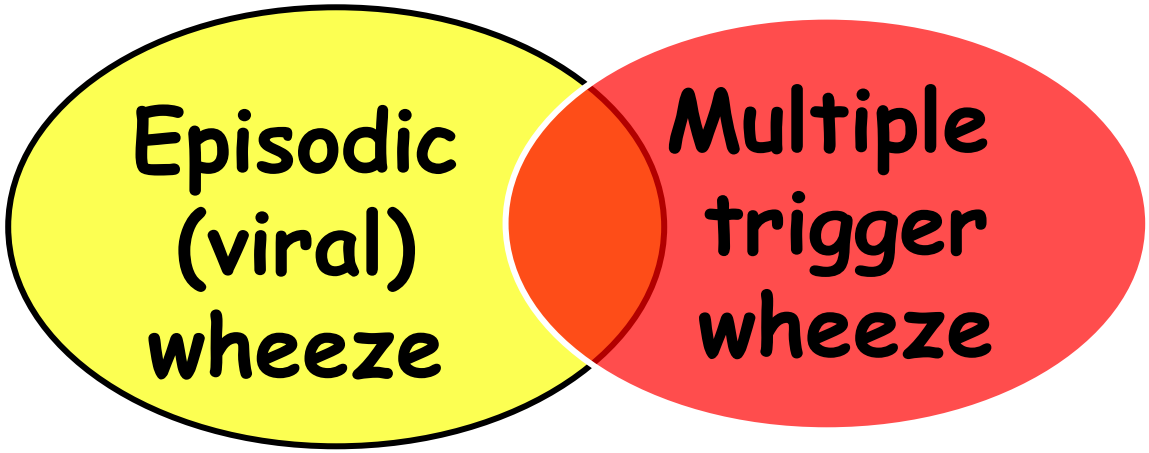
Children who wheeze intermittently and are well between episodes

Triggers: viruses

Wheeze both during and <u>between</u> exacerbations

Triggers: viruses, smoke, allergenes, exercise

PRESCHOOL WHEEZE - TREATMENT



Maintenance therapy

Intermittent therapy

Acute wheezing episodes

WHEN STARTING MAINTENANCE THERAPY ?

Regular controller treatment is suggested:

- The disease is not controlled
- Viral-induced episodes > 6 weeks
- Severe episodes
- Presence of risk factors ?

Treatment duration

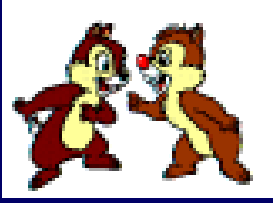
- Periods of 3 months

GINA 2009
ERS 2008
NAEPP 2007


TRATTAMENTO
CONTINUO CON
STEROIDI

The NEW ENGLAND JOURNAL of MEDICINE

PEAK STUDY



Early intervention with 2 years of fluticasone in young children (n=285) with 3 previous episodes of wheezing and HIGH RISK FOR ASTHMA

Age: 2-3 years old

- Parental history of asthma
- Atopic dermatitis
- Sensitization to 1 aeroallergen

RDB placebo controlled:

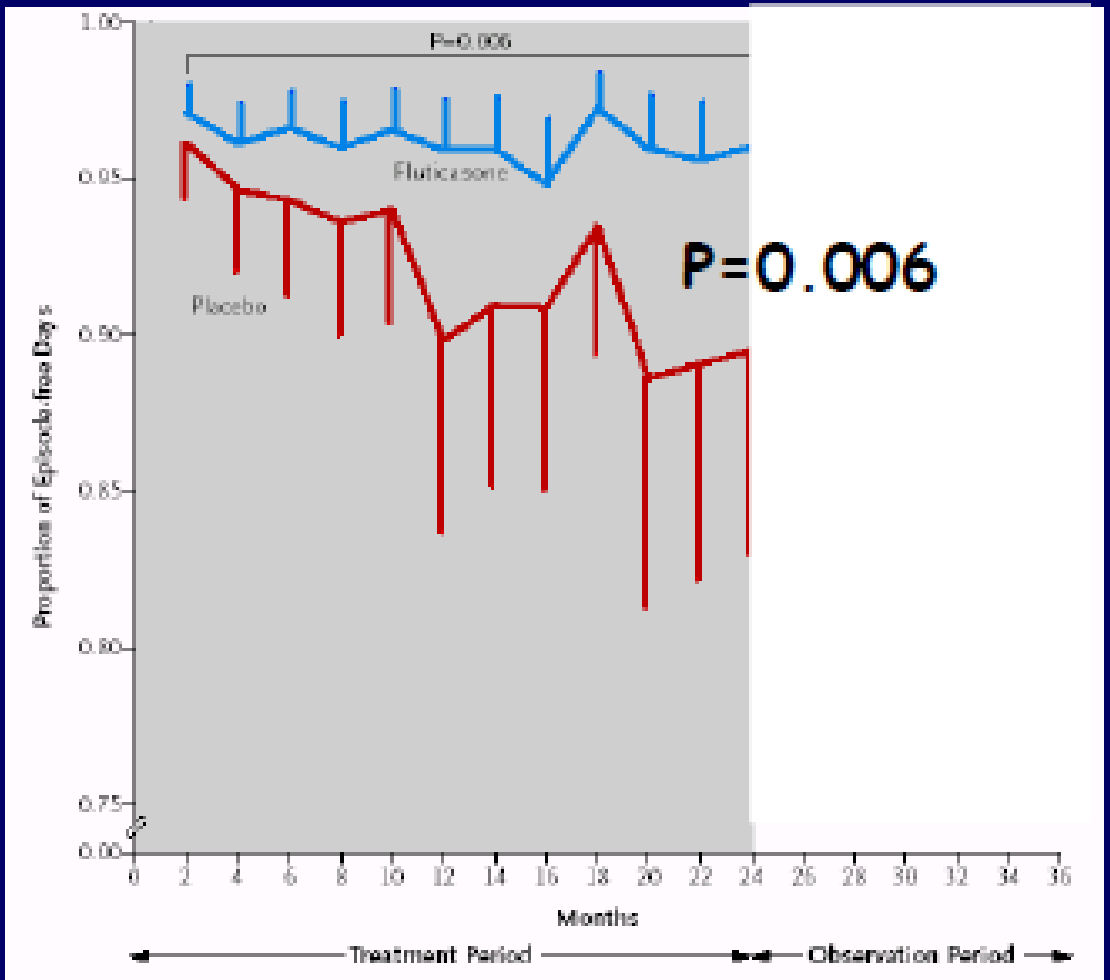
→ Fluticasone (88 mcg x 2)
→ placebo

for 2 years → 1 year observation

Guilbert NEJM 2006

PEAK STUDY

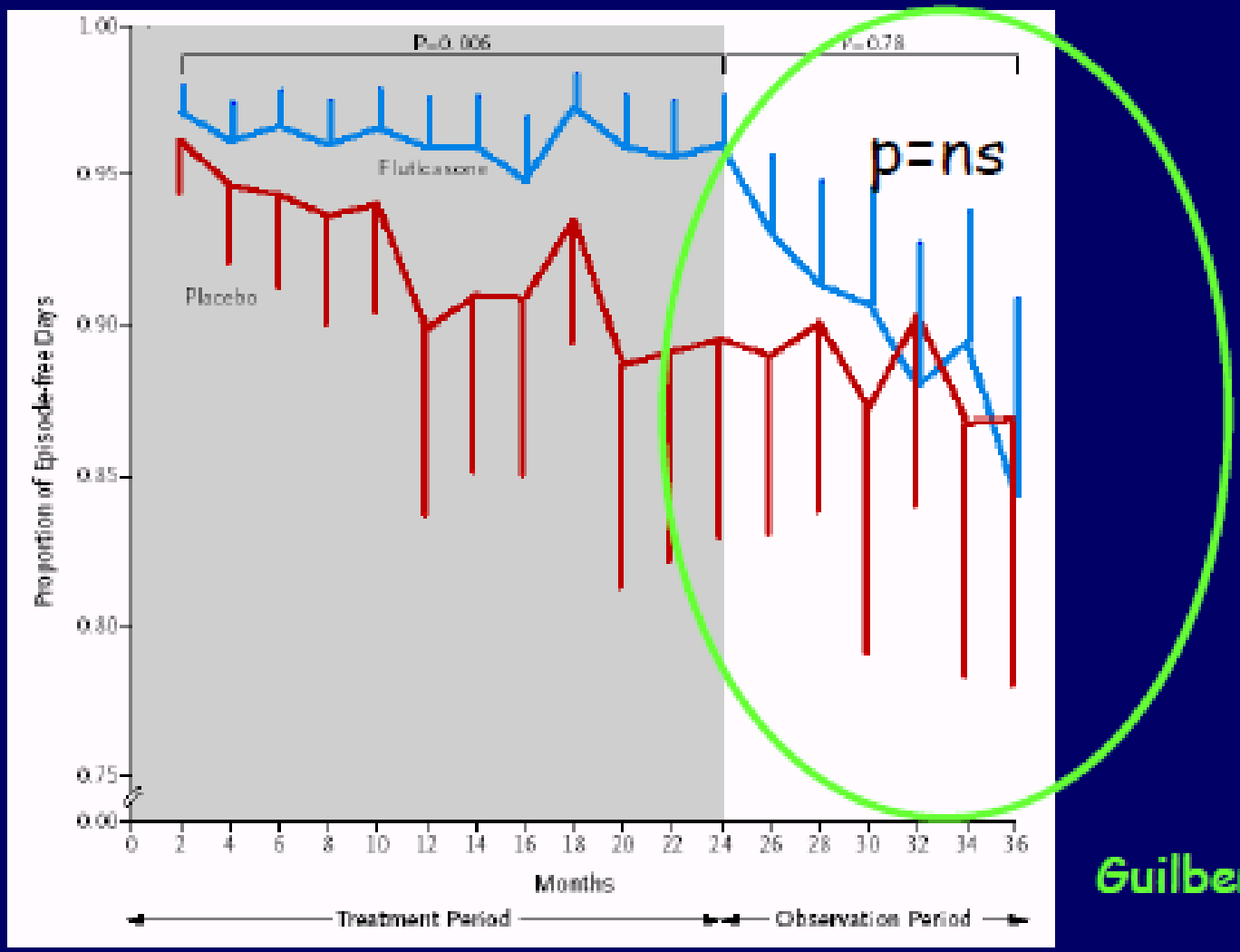
2 years of ICS in children at high risk for asthma reduced symptoms and exacerbations but.....



Guilbert NEJM 2006

PEAK STUDY

but <u>cannot</u> modify the natural history of asthma !



Guilbert NEJM 2006

ICS therapy

should not be used to prevent disease progression in children

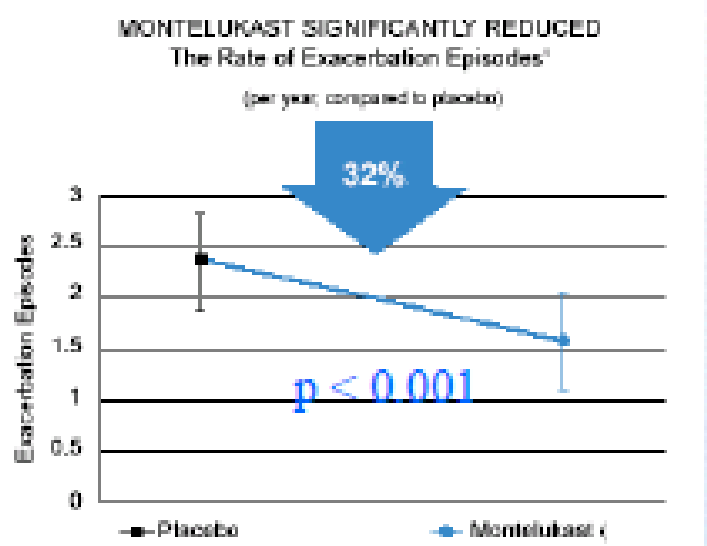
but rather to achieve symptom control and to reduce the risk of exacerbations

Horner COPM 2009

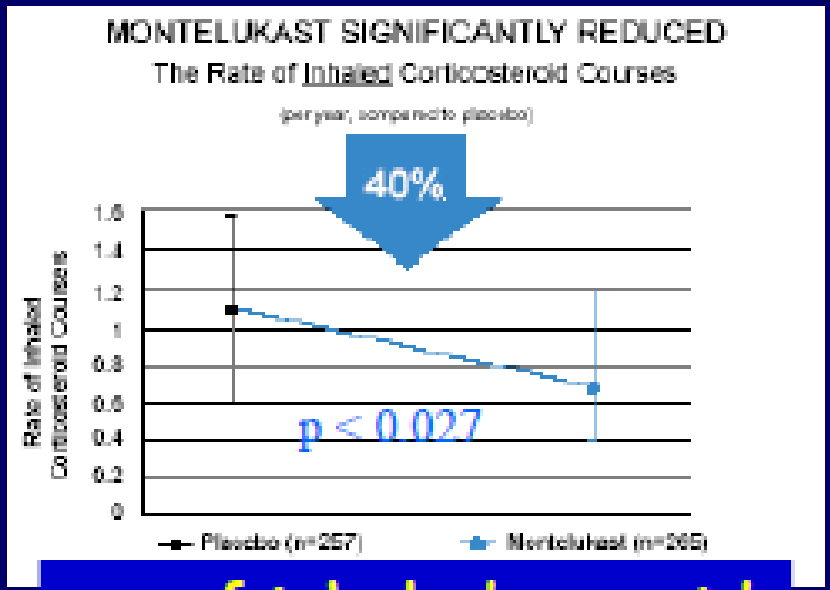

TRATTAMENTO
CONTINUO CON
MONTELUKAST

PREVIA "Prevention of Viral-Induced Asthma

- 549 children 2-5 years with recurrent wheezing
- placebo or montelukast (4 mg) for 1 year



rate of exacerbation/y

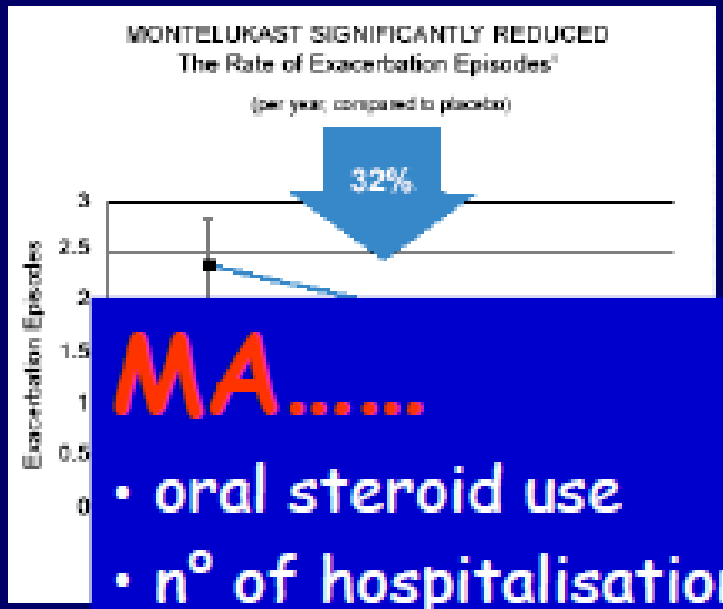


use of inhaled steroids

Bisgaard H Blue J 2005

PREVIA "Prevention of Viral-Induced Asthma

- 549 children 2-5 years with recurrent wheezing
- placebo or montelukast (4 mg) for 1 year



MA.....

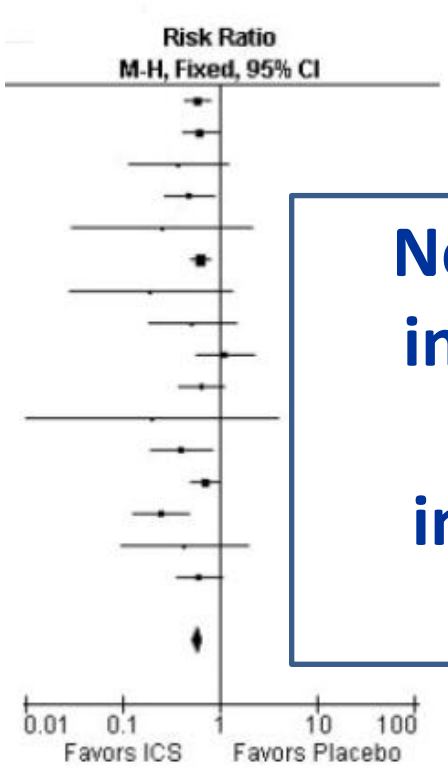
- oral steroid use
- n° of hospitalisations

} were similar among the 2 groups

Bisgaard AJRCCM 2005

Efficacy of Inhaled Corticosteroids in Infants and Preschoolers With Recurrent Wheezing and Asthma: A Systematic Review With Meta-analysis

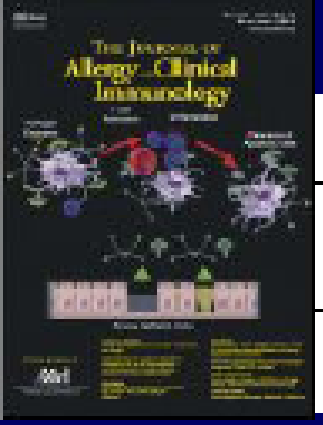
Jose A. Castro-Rodriguez, MD, PhD[a], Gustavo J. Rodrigo, MD[b]



This meta-analysis (29 studies, 3592 subjects)

Nel lattante con wheezing ricorrente i CS inalatori sono i piu' efficaci nel ridurre le esacerbazioni e le crisi gravi indipendentemente dai fattori di rischio associati

Castro-Rodriguez Pediatrics 2009



Perspectives in asthma

Understanding the September asthma epidemic

Malcolm R. Sears, FRACP,[a,b] and Neil W. Johnston, MSc[b] *Hamilton, Ontario, Canada*

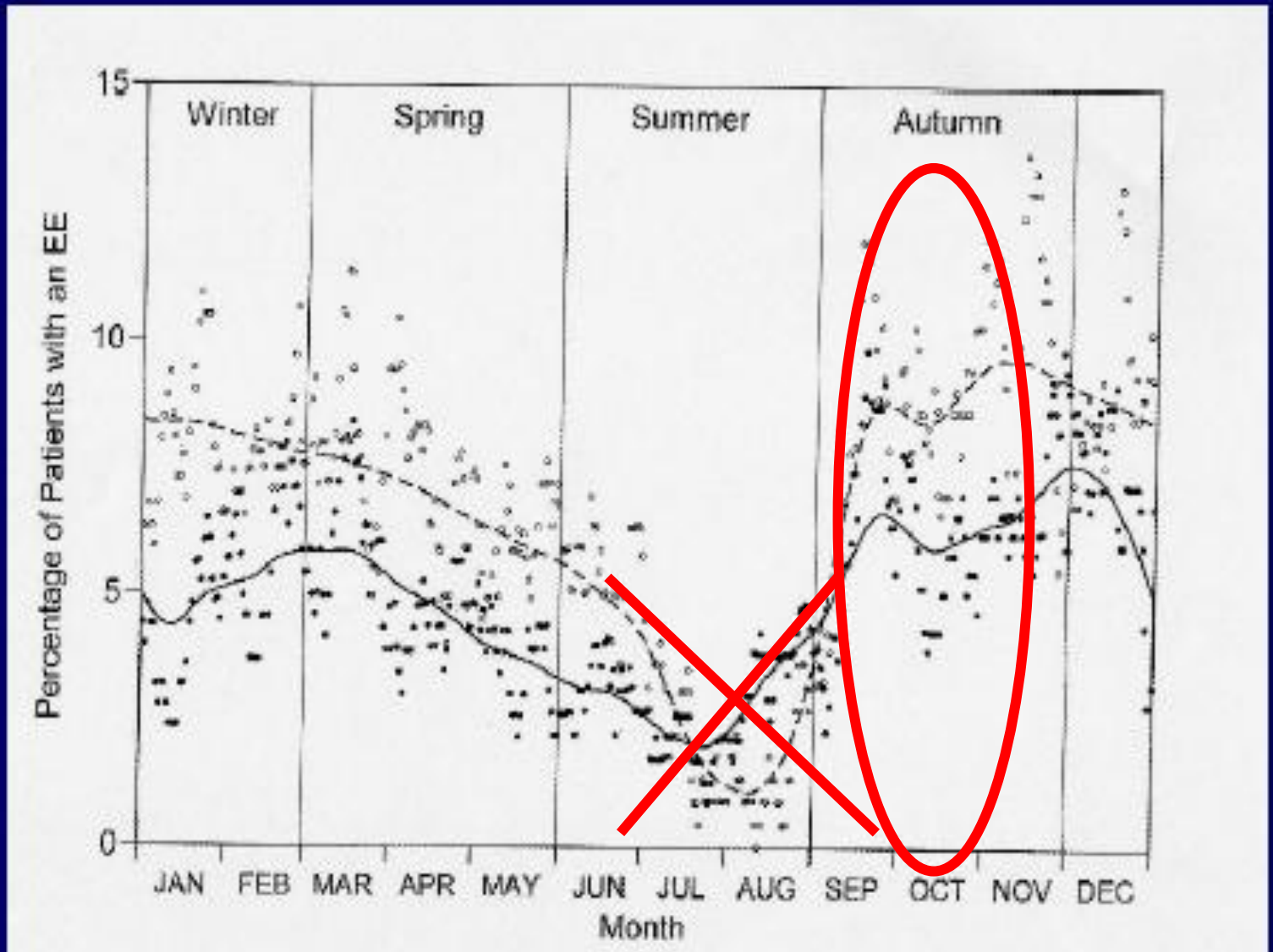
- Dal 20 al 25% dei ricoveri per riacutizzazioni asmatiche avvengono in Settembre

- Le riacutizzazioni di Settembre si associano, in circa l'80% dei casi, ad infezioni virali in prevalenza da rinovirus

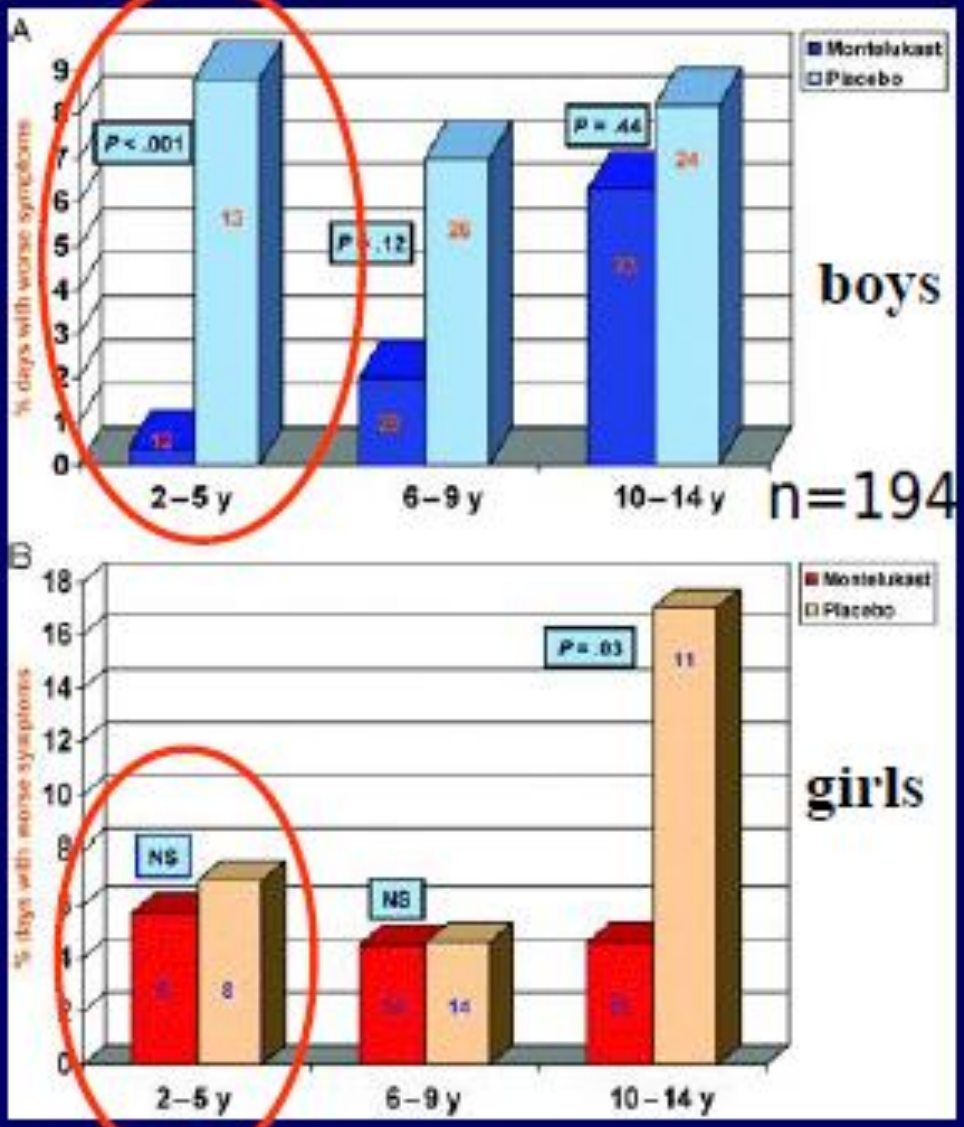
- Un inadeguato trattamento con farmaci anti-asmatici di controllo in Settembre favorisce le riacutizzazioni

JACI 2007; ;120:526

Daily % of children with an exacerbation episode



Attenuation of the September epidemic of asthma exacerbations: montelukast added to usual therapy



MA

Boys 2-5 yrs greater benefit !

Johnston et al Pediatrics 2007

Principali modifiche del report di strategia GINA 2015 Update (2)

- Inalatori di polveri secche possono essere usati per somministrare SABA in riacutizzazioni lievi o moderate
  - Non attuare in pazienti con asma grave acuta

- Asma grave acuta o quasi-mortale in assistenza primaria
  - Mentre si organizza le procedure di terapia intensiva, somministrare ipratropio bromuro nonché SABA, OCS e ossigeno.

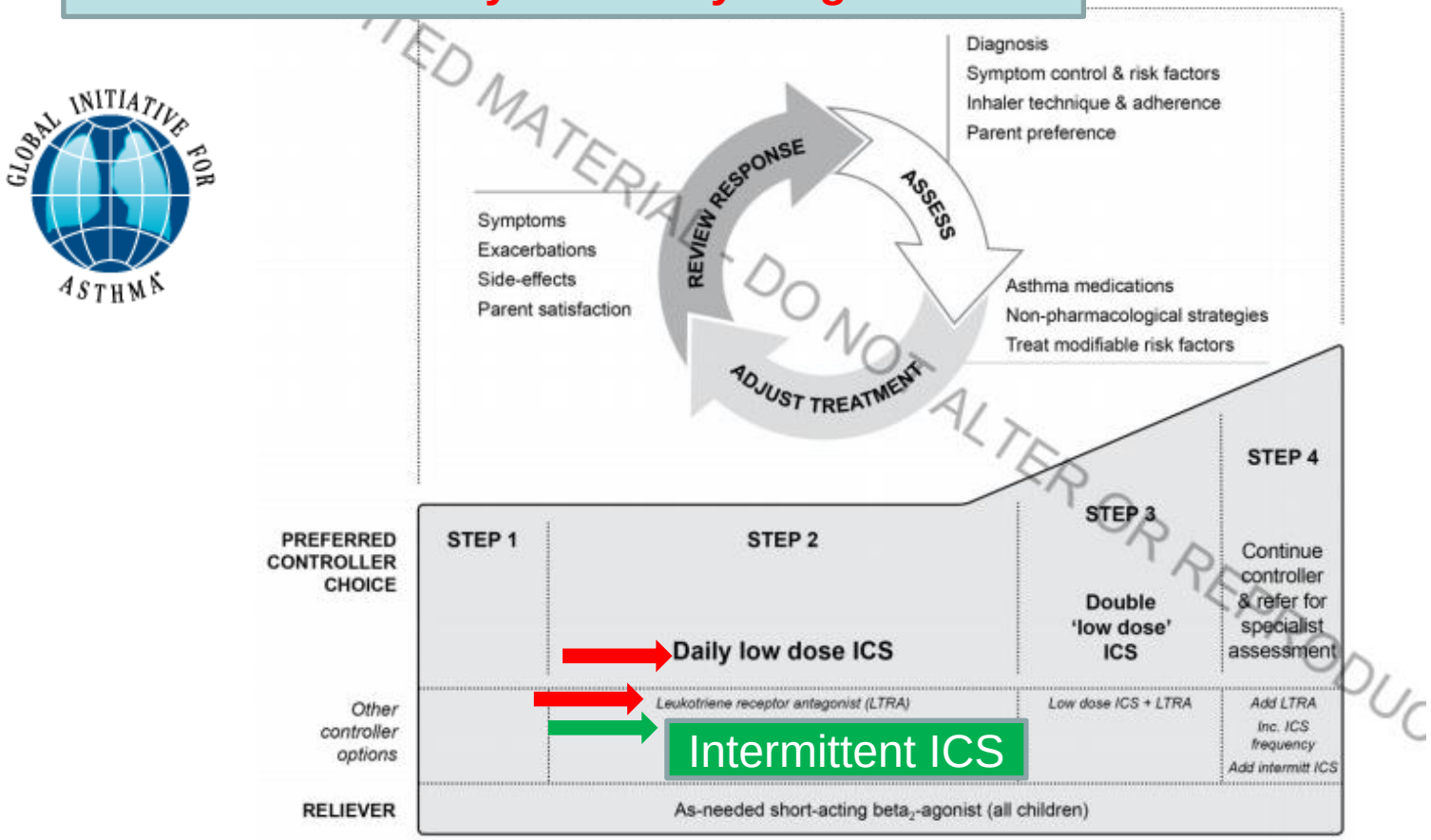
- Bambini in età prescolare con crisi asmatiche o episodi di sibilo
  - Non è raccomandata in genere la somministrazione di OCS o alte dosi di ICS
    - Visto che sibili e infezioni delle vie respiratorie si verificano molto frequentemente, vi è preoccupazione per il rischio di effetti collaterli sistemici
  - Vi è una nuova flow chart per la gestione delle crisi asmatiche e dei sibili.

Corticosteroidi inalatori nell'asma lieve persistente

Daily vs Intermittent

Stepway approach to asthma treatment in children 5 years and younger

GINA guidelines 2014



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ESTABLISHED IN 1812 MAY 11, 2006 VOL. 354 NO. 19

Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing

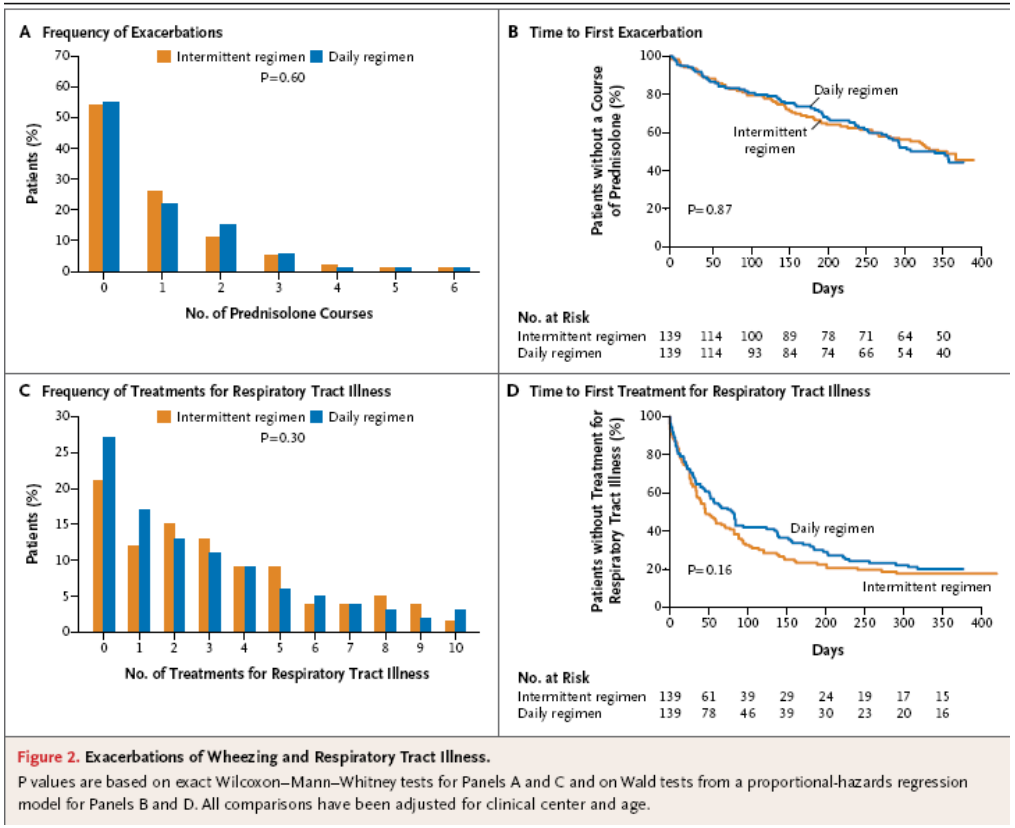

Figure 2. Exacerbations of Wheezing and Respiratory Tract Illness.
P values are based on exact Wilcoxon–Mann–Whitney tests for Panels A and C and on Wald tests from a proportional-hazards regression model for Panels B and D. All comparisons have been adjusted for clinical center and age.

- **CARE Network-MIST**
- **National Heart, Lung, Blood Institute**

Age: 12-53 months
n=278
API+, recurrent wheeze and exacerbations

Budesonide-neb

- 0.5 mg/day **1 year**
- 1mgX2 day **7 days**

Zeiger NEJM 2011

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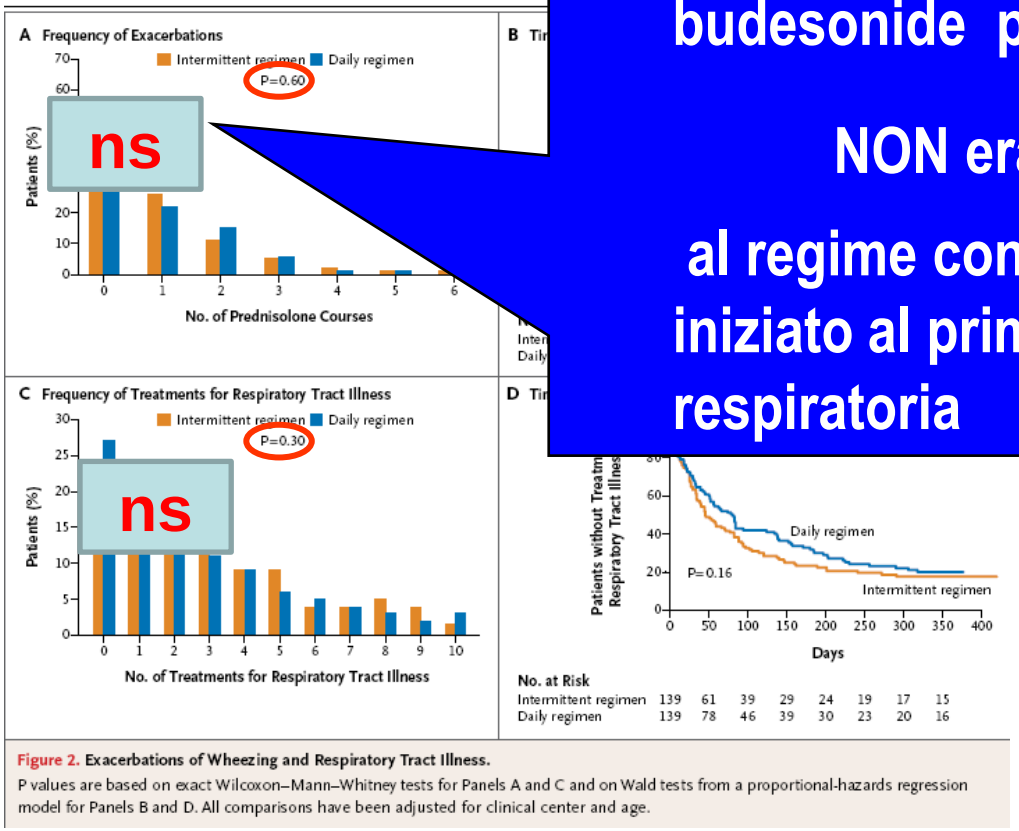
in P

RIACUTIZZAZIONI

Una bassa dose giornaliera di budesonide per un anno

NON era superiore

al regime con alte dosi intermittenti iniziato al primo segno di infezione respiratoria



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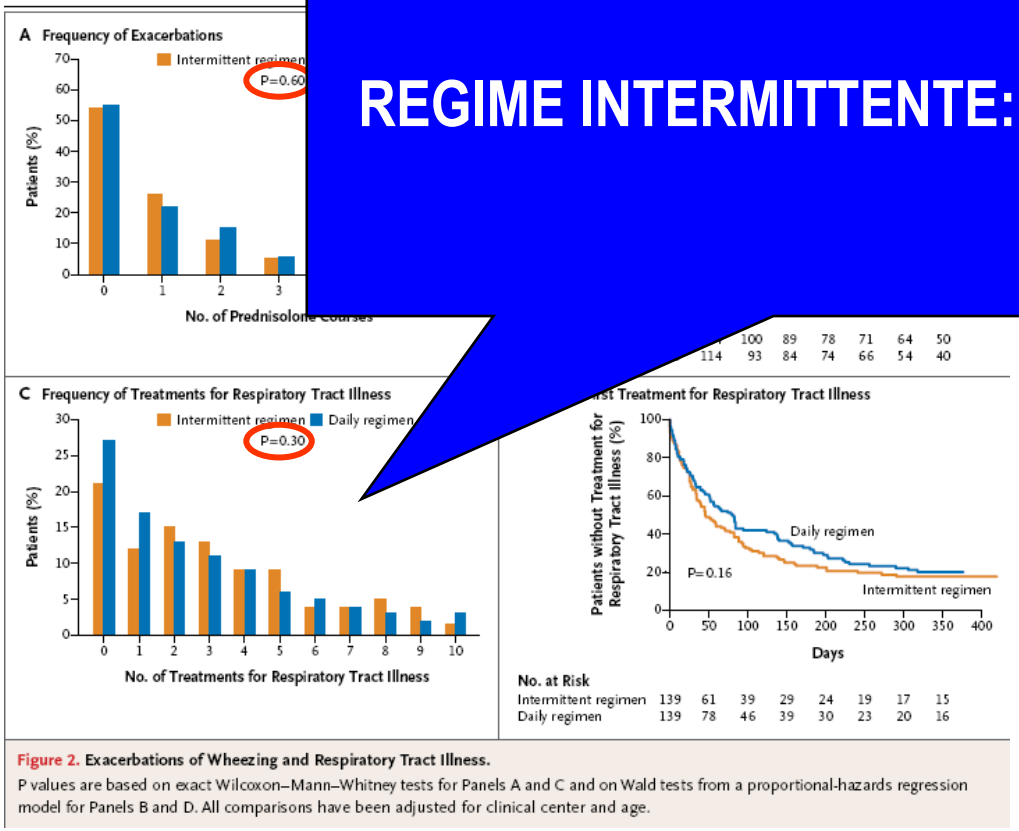
DOSE totale di ICS

REGIME GIORNALIERO: 150 mg/12 mesi

REGIME INTERMITTENTE: 46 mg/12 mesi

ezing

twork-MIST
Heart, Lung,
stitute



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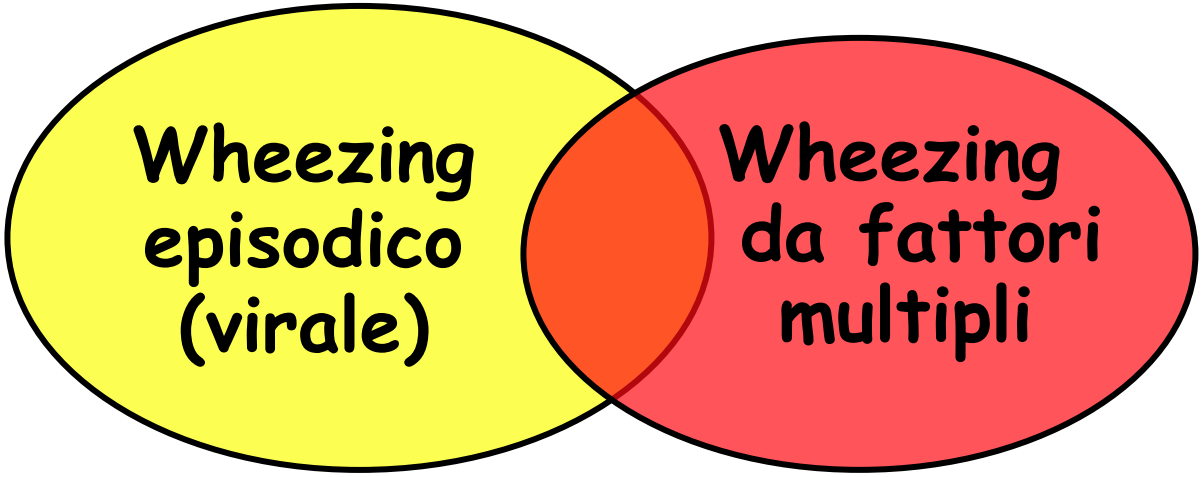
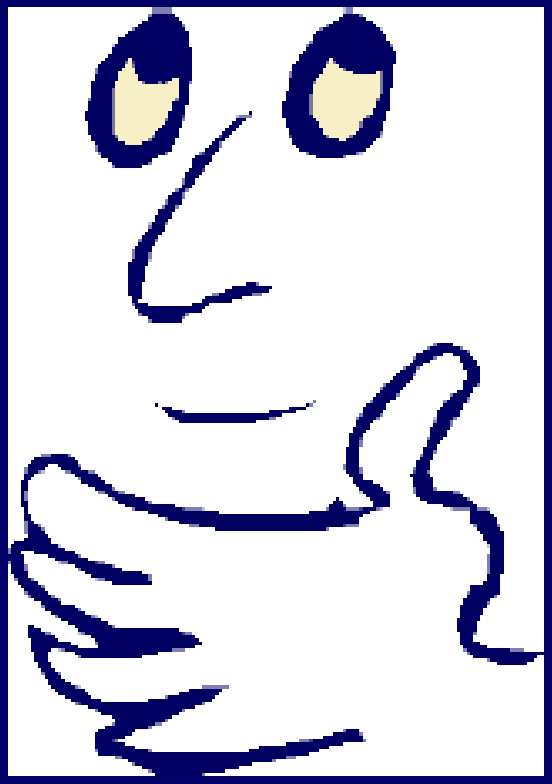
Wheezing in età prescolare



Terapia intermittente con alte dosi di ICS

7-10 GIORNI DI TERAPIA AD ALTE DOSI CON ICS ASSOCIATA AL SALBUTAMOLO INIZIATA AL PRIMO SEGNO DI INFEZIONE RESPIRATORIA



quello che pensavamo di sapere e che invece dobbiamo ripensare……..

Wheezing

is a symptom/chest sound

and not a diagnosis !

Salbutamolo per periodi prolungati
Steroidi inalatori a cicli di almeno 3 mesi
Antileucotrieni a cicli di almeno 3 mesi)
Steroidi sistemici

Salbutamolo al bisogno x brevi periodi
Steroidi inalatori intermittenti
Antileucotrieni intermittenti

AIRWAY INFLAMMATION IS HETEROGENEOUS

Traditional strategy

One therapy fits all

Personalized strategy

One fits one

WHEEZING PHENOTYPES

Bambini in eta' prescolare con wheezing ricorrente

Diagnosis of

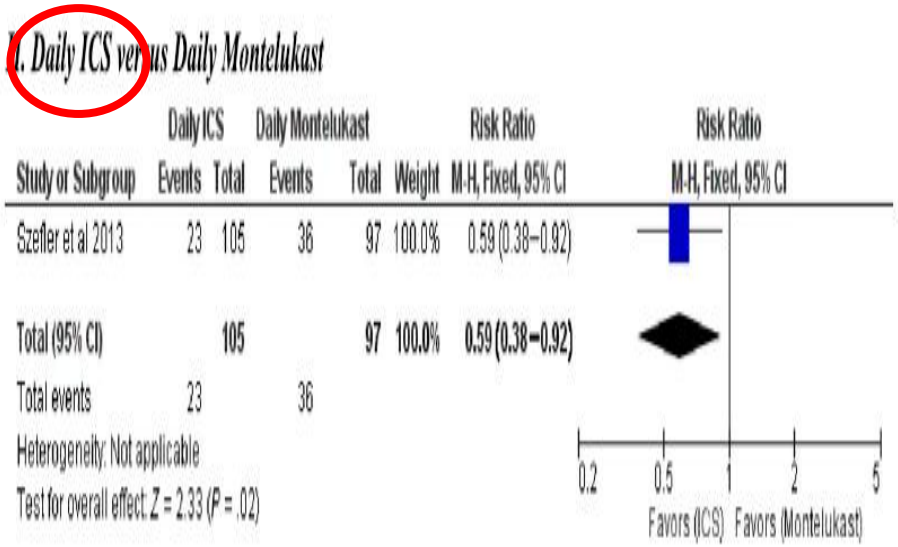
Bambini in eta' prescolare con asma intermittente o con viral-triggers wheezing

Bambini in eta' prescolare con asma persistente

Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis

Sunitha V. Kaiser, MD, MSc,[a] Tram Huynh,[b] Leonard B. Bachar
[d] Leigh Anne Bakel, MD,[e] Patricia C. Parkin, MD, FRCPC,[f] Micha

Bambini in eta' prescolare con wheezing ricorrente



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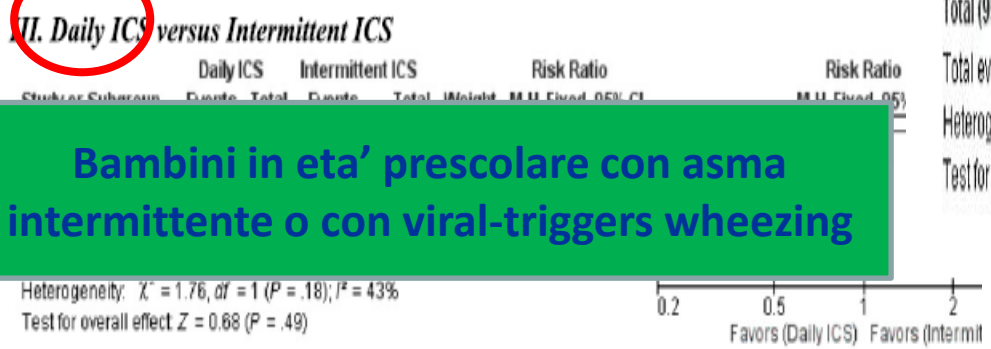
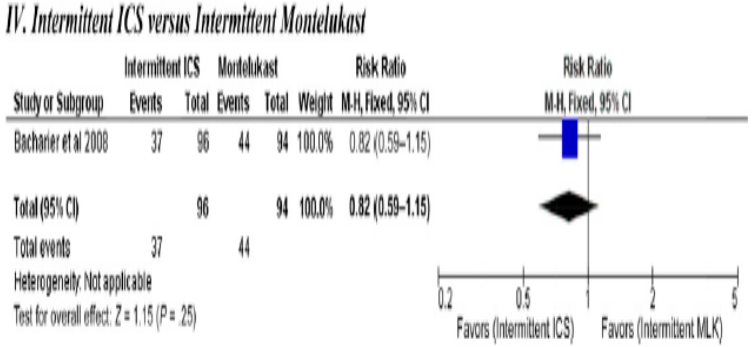
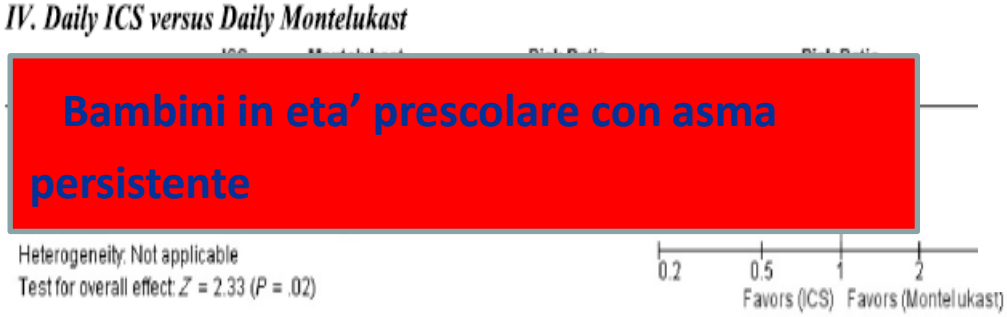




Bambini in eta' prescolare con asma persistente



Key messages

- La **terapia giornaliera prolungata con ICS a basse dosi** sembra essere la piu' efficace per i bambini con **wheezing ricorrente** che presentano sintomi fra gli episodi acuti o atopia.

- La **terapia intermittente con ICS ad alte dosi** e' risultata efficace nei bambini con **wheezing intermittente** o indotto da infezioni virali che sono asintomatici tra le riacutizzazioni

- La terapia con **Montelukast** in concomitanza con il periodo piu' critico per le infezioni virali sembre ridurre le **riacutizzazioni asmatiche stagionali**

Diagnosis, management, and prognosis of preschool wheeze

IL WHEEZING RICORRENTE: UN UNICO SUONO PER MOLTI STRUMENTI

SALVATORE LEONARDI
U.O.C DI BRONCOPNEUMOLOGIA PEDIATRICA

COMISO 10 FEBBRAIO 6017

Grazie dell'attenzione

Percorsi Pediatrici Simeto-Etna 2016

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CONCLUSIONS: There is strong evidence to support daily ICS for preventing exacerbations in preschool children with recurrent wheeze, specifically in children with persistent asthma. For preschool children with intermittent asthma or viral-triggered wheezing, there is strong evidence to support intermittent ICS for preventing exacerbations.