XIX Congresso Nazionale
Società Italiana di Pediatria
Preventiva e Sociale

Gestire i cambiamenti
per prevenire

on il patrocinio del Ministero della Salute

26 - 28 Ottobre 2007

Hotel Atlantic - Torino

Asma e infezioni

Michele Miraglia del Giudice

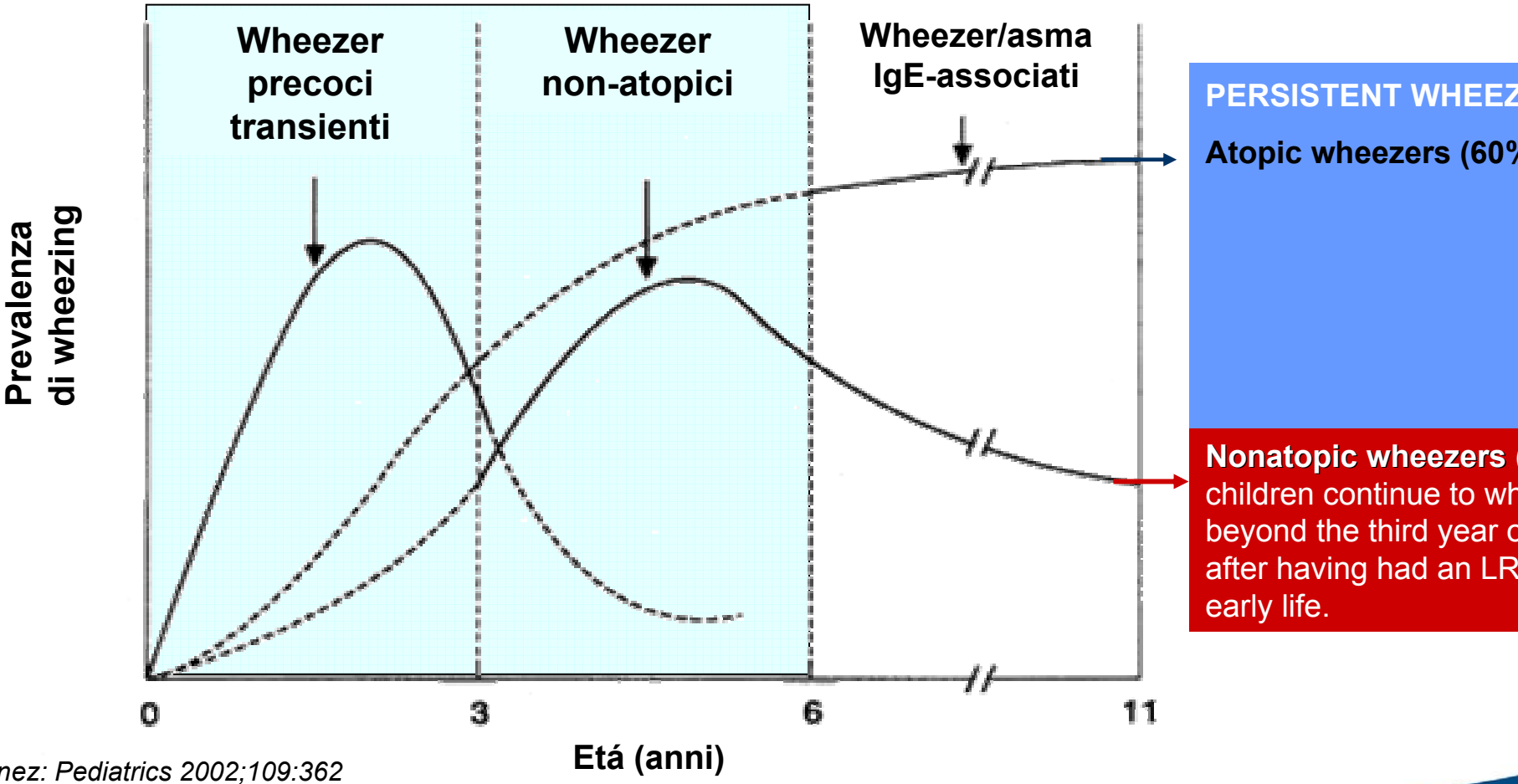
Servizio Speciale Autonomo Asma e Fisiopatologia Respiratoria Infan

"Maurizio Miraglia del Giudice"

Dipartimento di Pediatria

Seconda Università di Napoli

fferenti fenotipi di wheezing
età pediatrica e relativa prevalenza



nez: Pediatrics 2002;109:362

acutizzazioni asmatiche e virus respiratori

e infezioni virali sono causa frequente
i riacutizzazioni asmatiche

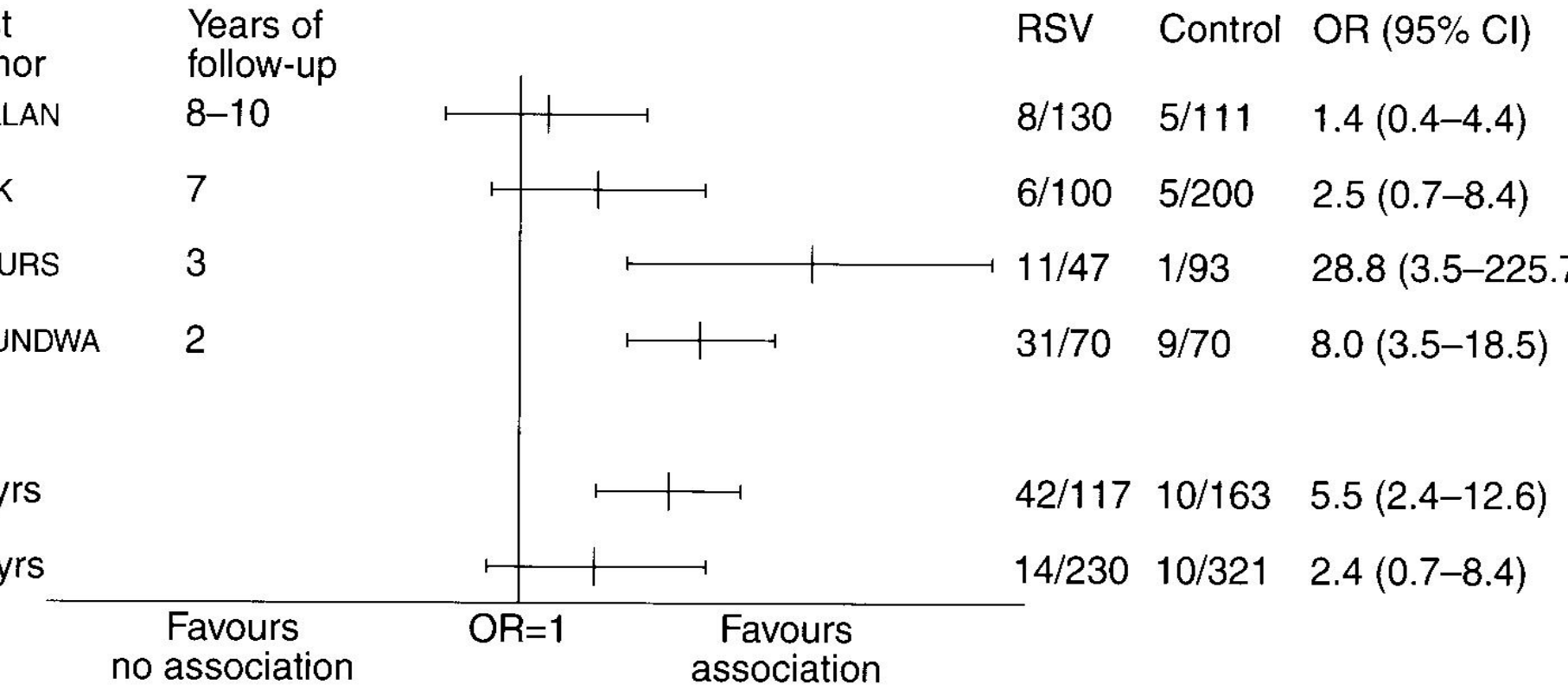
soggetti asmatici sono più suscettibili
ll'infezione da rinovirus

E dimostrato un sinergismo tra infezioni virali
d esposizione ad allergeni nell'indurre
e riacutizzazioni e nel determinare la gravità
elle riacutizzazioni

Respiratory syncitial virus is the most important agent causing acute respiratory infections in children aged under two years.

Hall CB J Infect Dis 1990

RSV bronchiolitis and recurrent wheezing



–Relationship between respiratory syncytial virus (RSV) bronchiolitis in infancy and recurrent whee
childhood. Odds ratios (OR) with 95% confidence interval (CI) are indicated. No significant differ
n the RSV bronchiolitis and the control group is seen by 5 yrs of follow-up. The solid vertical line re
R=1.

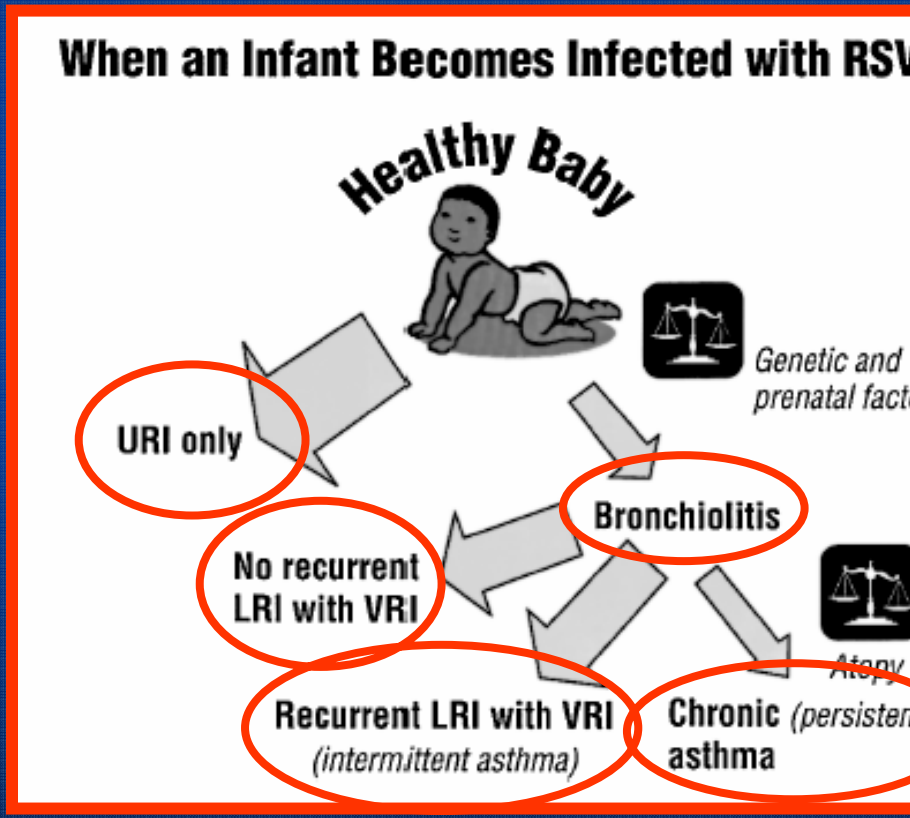
Kneyber MCJ et al. – Acta Paediatr., 2000, 89,65

INICAL PATTERNS AND NATURAL HISTORY OF THMA

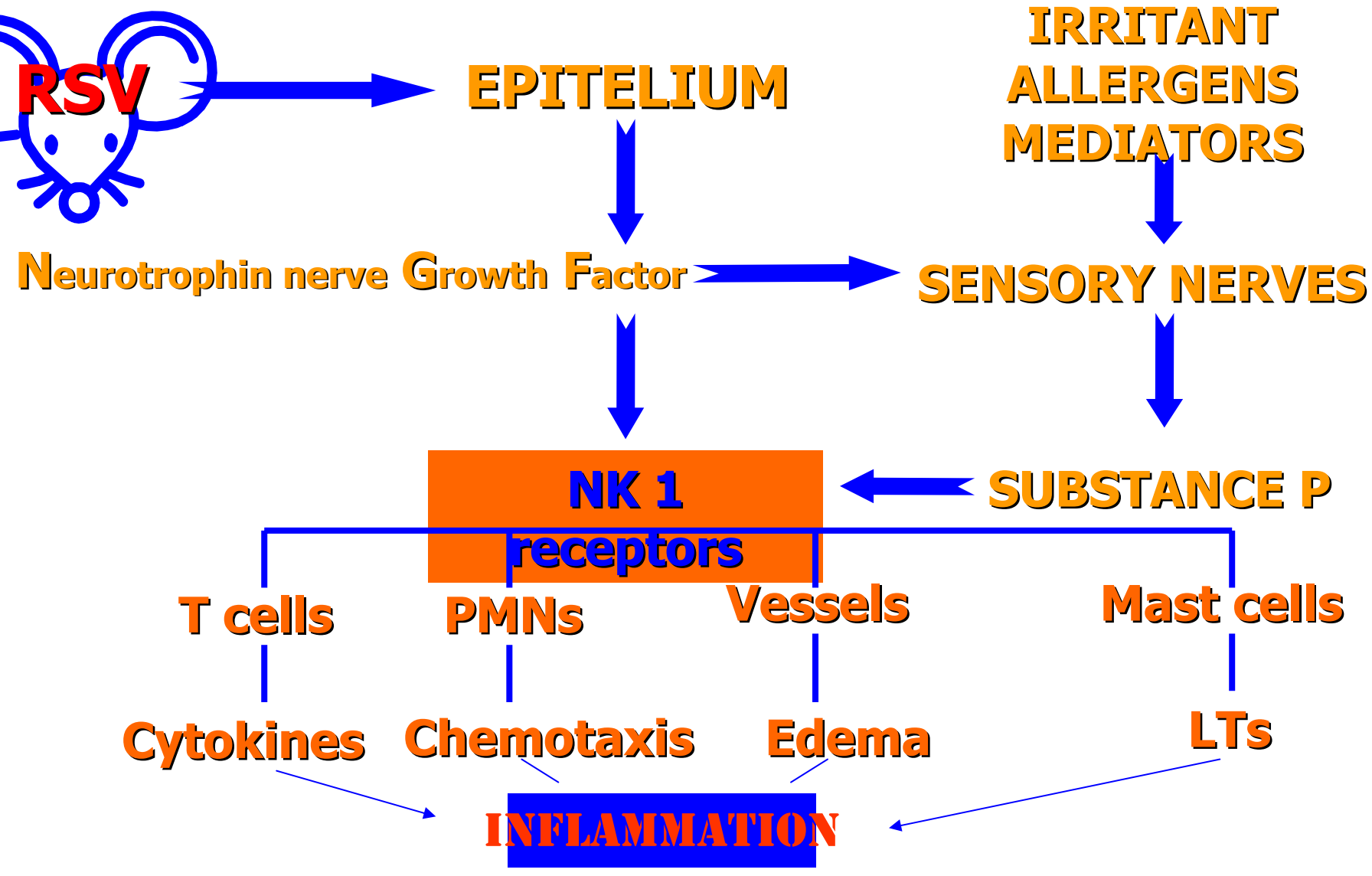
einberger – J Pediatr 2003;142:S15- S20

Clinical experience and natural history studies suggest that:

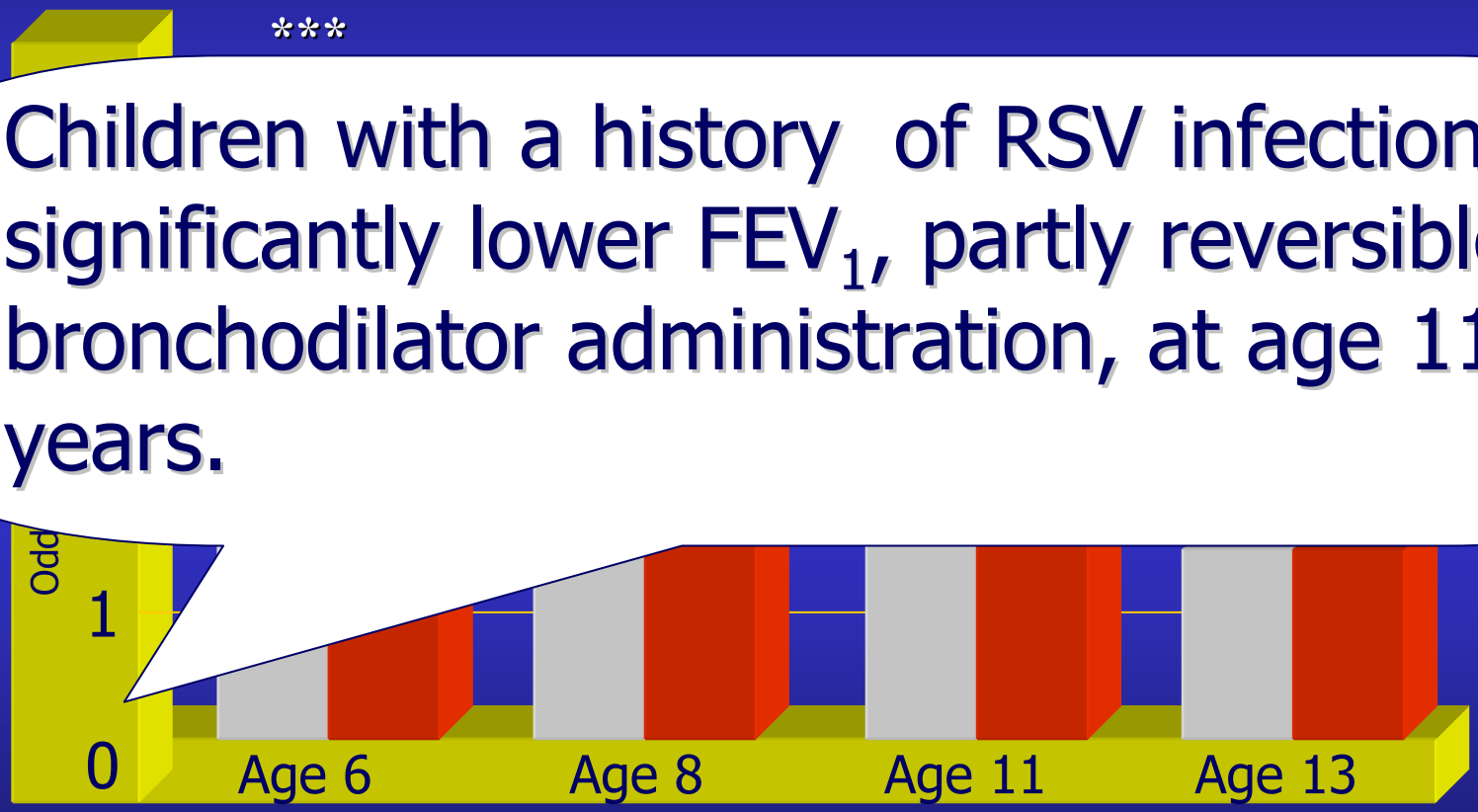
- the majority of such children lose their symptoms later in childhood
- about 25% to 50% subsequently have symptoms of asthma manifested by recurrent wheezing in association with VRI
- some continue to have chronic lower airway disease from asthma throughout childhood
- some remain symptomatic into adult life



ro inflammatory interactions and neural odelling in RSV-infected airway *da Piedimonte G. 200*



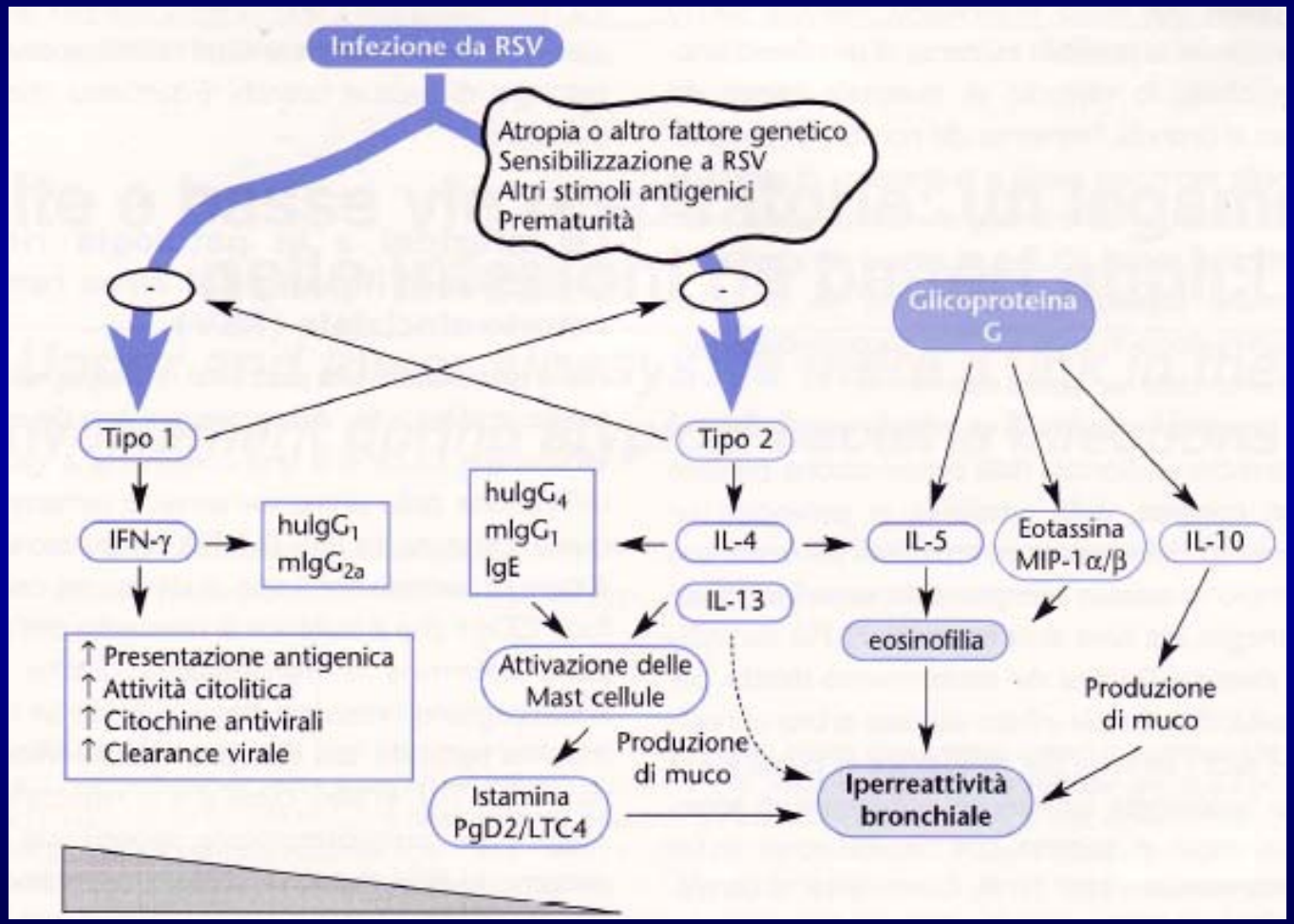
risk of frequent and infrequent wheeze in dren who had mild-moderate RSV LRTI



Children with a history of RSV infection had significantly lower FEV_1, partly reversible by bronchodilator administration, at age 11 years.

*** p < 0,001 ** p < 0,01 * p < 0,05

Stein LT. Lancet



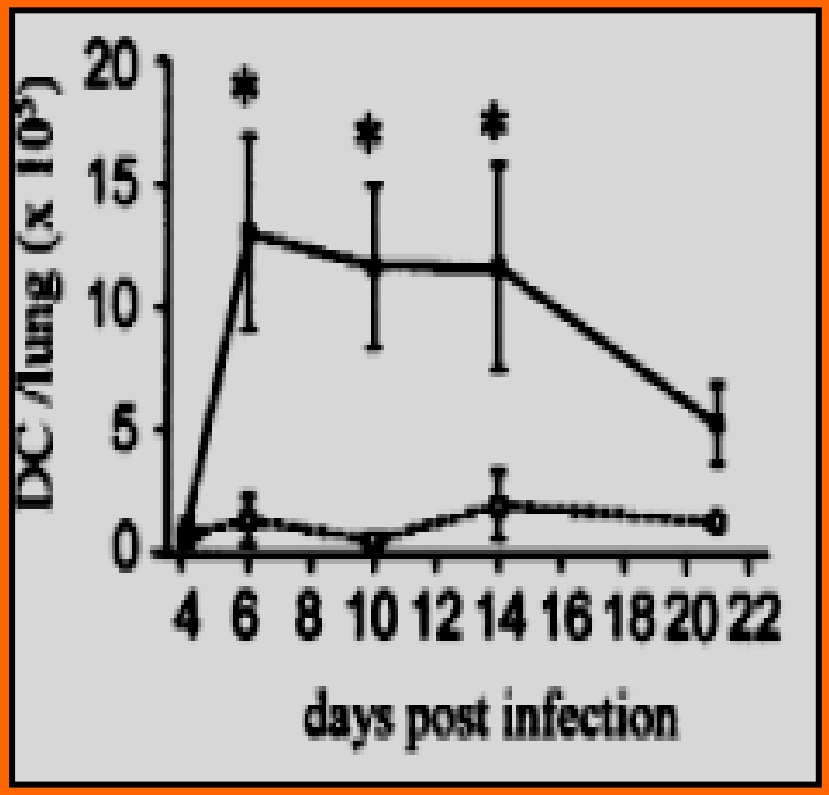
da Graham BS. 2000

Sustained increases in numbers of pulmonary dendritic cells after respiratory syncytial virus infection

Marc Beyer-J Allergy Clin Immunol 2004;113:127-33

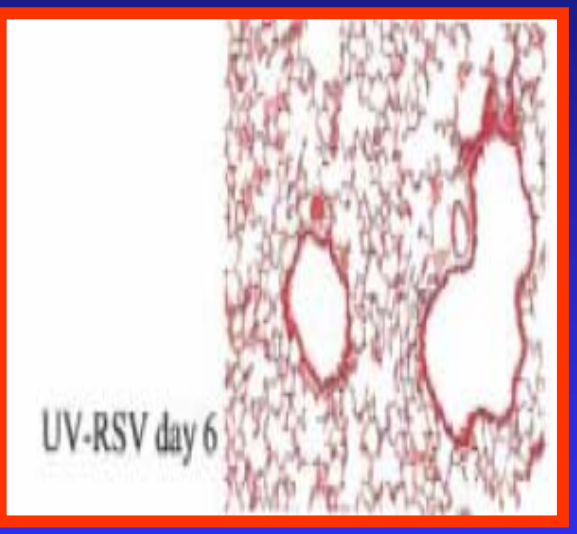
RSV infection results in sustained increases in numbers of mature dendritic cells in the lung.

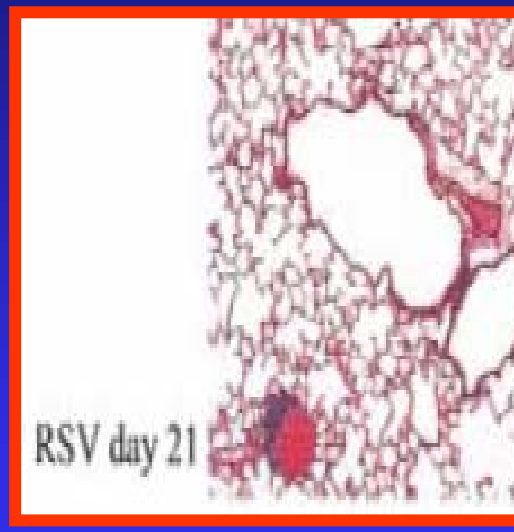
These might well contribute to the development of intense airway inflammation and airway hyperresponsiveness after RSV Infection and <u>to enhancement of subsequent responses to allergen exposure.</u>



stained increases in numbers of pulmonary dendrit
ls after respiratory syncytial virus infection

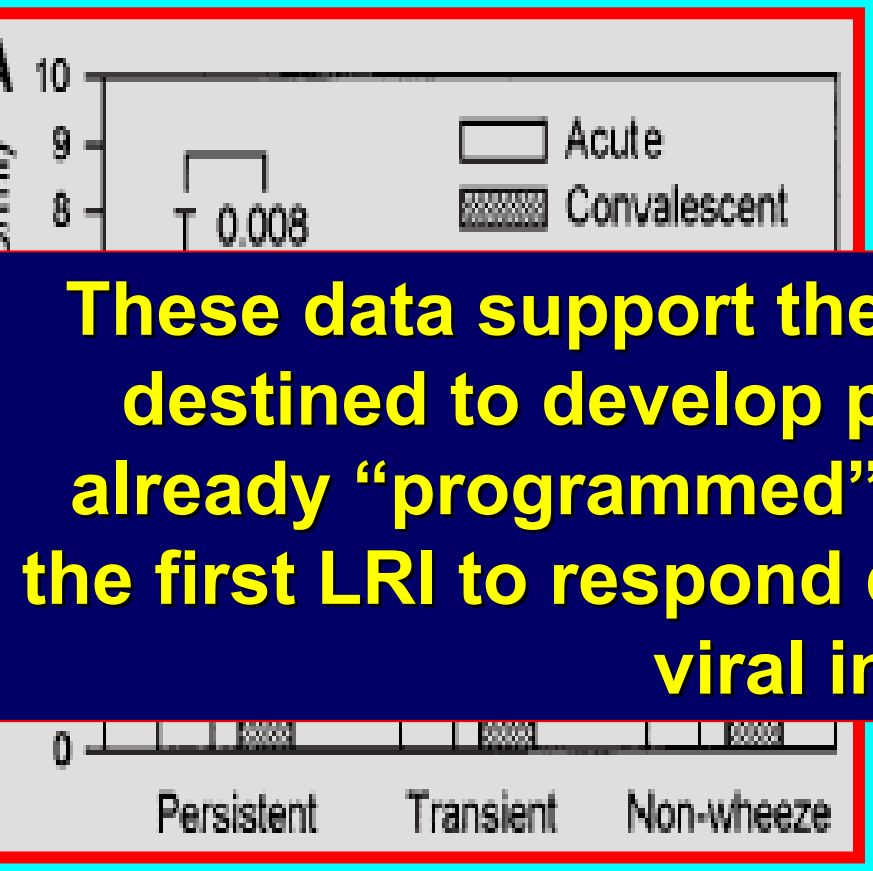
c Beyer-J Allergy Clin Immunol 2004;113:127-33

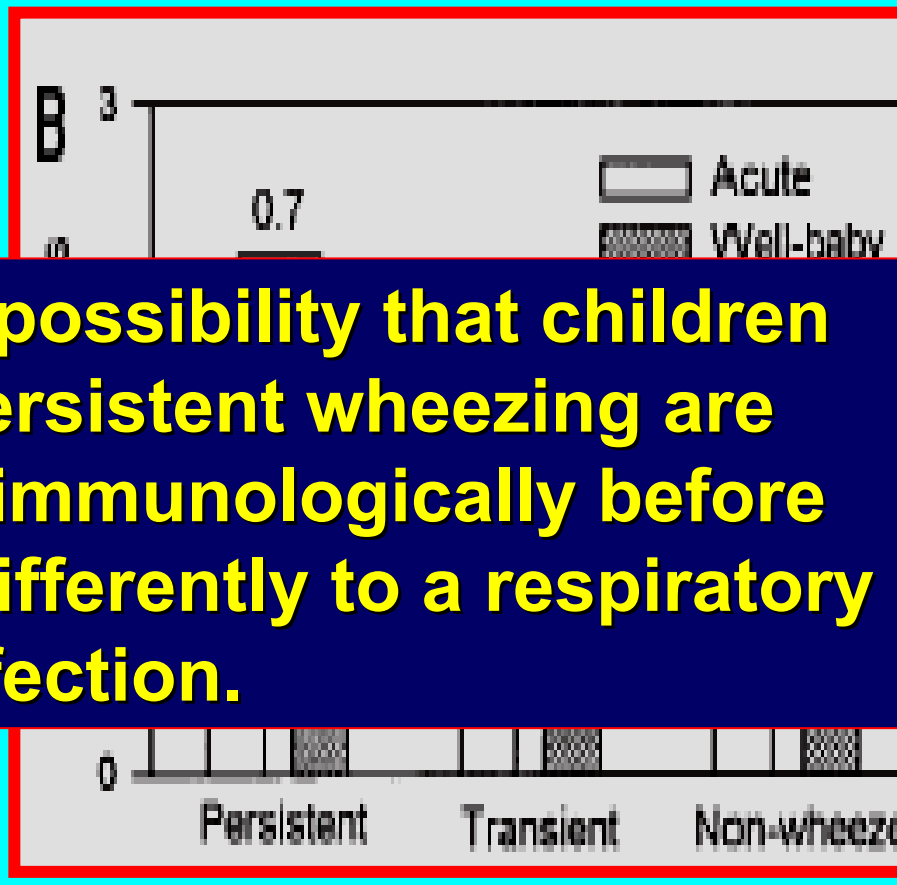




Low dose RSV infection results in peribronchial and perivascular inflammation in the lu
mice were infected with RSV or UV-RSV(RSV inactivated by ultraviolet light) and killed
6 and 21 days.

Differences in total serum IgE (A) and peripheral blood *(PB)* osinophil levels (B) during and after the first LRI for children group as to their subsequent age 6 wheezing patterns.





These data support the possibility that children destined to develop persistent wheezing are already "programmed" immunologically before the first LRI to respond differently to a respiratory viral infection.

Palivizumab Prophylaxis, Respiratory Syncytial Virus, an Subsequent Recurrent Wheezing

Simoes E et al. J Pediatr 2007;151:34-42

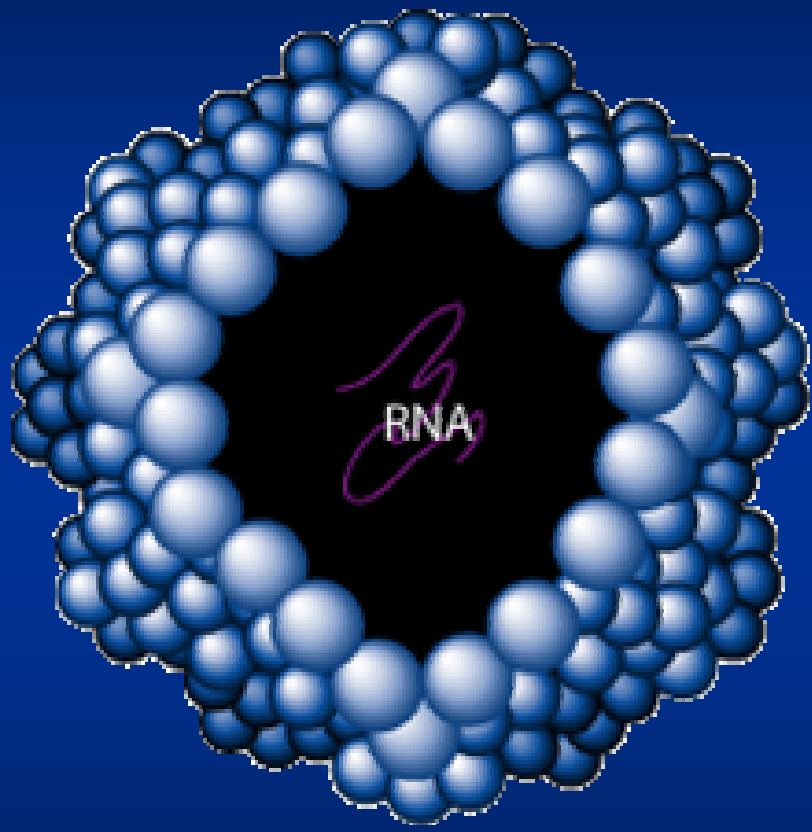
cohort of preterm infants who had received palivizumab and were not pitalized for RSV (n 191) or who never received palivizumab (n 230; were hospitalized for RSV and 154 who were not), were prospectiv

Preventing RSV LRTI with palivizumab may reduce subsequent recurrent wheezing in premature infants

e rent
e ects (1

8%, respectively) compared with all 230 untreated subjects (26%, P .
16%, P 0.011, respectively) and with the 154 patients in the subgroup
pitalized for RSV LRTI (23%, P 0.022 and 16%, P 0.027, respectively)

Rhinovirus is a genus of the *Picornaviridae* family of viruses. Rhinoviruses are the most common viral infective agents in humans, and a causative agent of the common cold. There are over 105 serologic virus types that cause cold symptoms, and rhinoviruses are responsible for approximately 50% of all cases. Rhinoviruses have single-stranded positive sense RNA genomes.

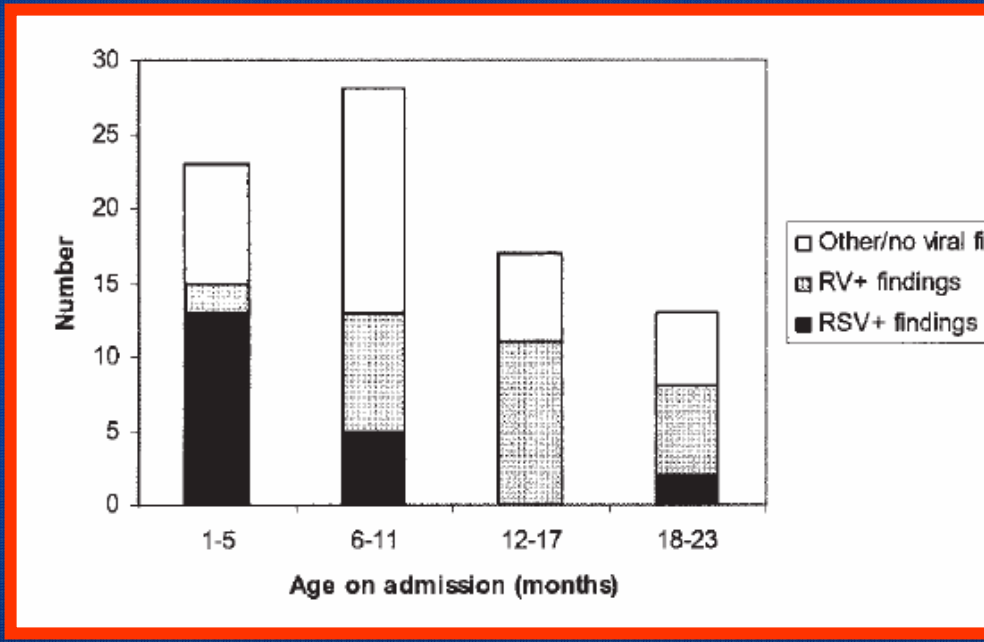


inovirus-induced wheezing in infancy - the first n of childhood asthma?

taniemi-Syrjänen, R. Vainionpää et coll – JACI 2003;111:66-71

82 CHILDREN WHO HAD BEEN HOSPITALIZED FOR WHEEZING

- Under the age of 6 months the most common viral finding was RSV.
- From the age of 6 months RVs were the most prevalent of the respiratory viruses identified
- Infants with atopic dermatitis were especially likely to wheeze during RV infection.
- Hospitalization for RV-induced wheezing in infancy was significantly associated with early school-age asthma (more than 4-fold)



RV-induced wheezing leading to hospitalization seems to predict the development of asthma

quency, severity, and duration of rhinovirus infections sthmatic and non-asthmatic individuals: a longitudinal ort study

orne, C Marshall, S Smith et coll – Lancet 2002;359:831-34

ndividuals with asthma are not at ncreased risk of rhinovirus nfection but **have LRT clinical lness twice as frequently, more evere and long lasting LRT ymptoms** when infected by hinovirus than do healthy ndividuals.

he effects of rhinovirus infection n the frequency of URT clinical lness and on the severity and uration of all symptoms ssociated with infection were imilar in individuals with and vithout asthma.

Symptoms	Participants with asthma (n=76)	Healthy particip (n=76)
URT		
Severity (score)	2 (0–12)	2 (0–7)
Duration (days)	3·5 (0–11)	3 (0–17)
LRT		
Severity (score)	1 (0–17)	0 (0–7)*
Duration (days)	2·5 (0–35)	0 (0–22)†

Data are median (range). *p=0·001. †p=0·005.

Severity and duration of upper-respiratory-tract (URT) and lower-respiratory-tract (LRT) symptoms associated with rhinovirus infection

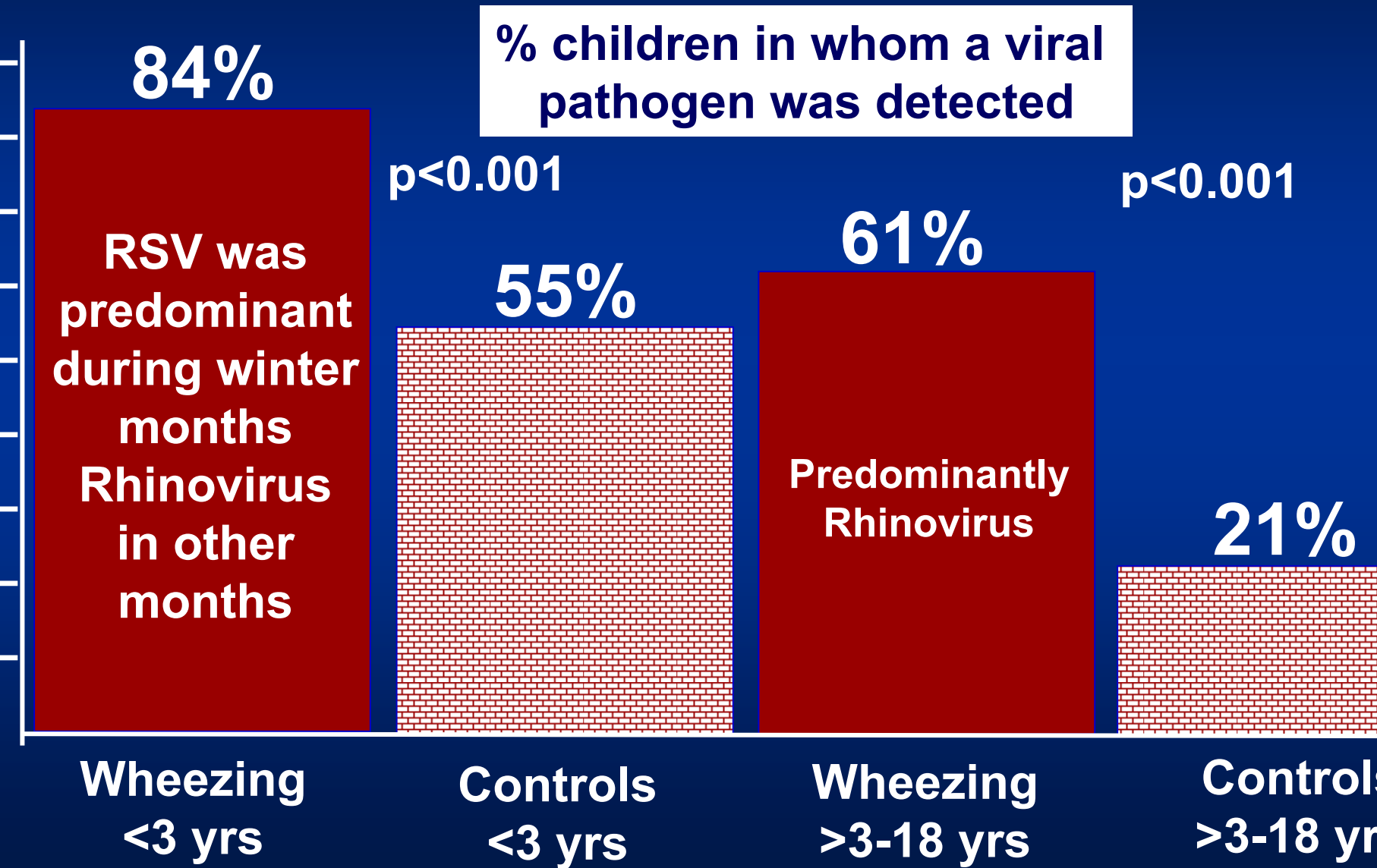
RAL INFECTIONS IN RELATION TO AGE, ATOPY, AND SEASON O ADMISSION AMONG CHILDREN HOSPITALIZED FOR WHEEZING

Heymann JACI 2004; 114: 239

- Case control study of children (age 2 months to 18 yrs) admitted for wheezing over a period of 12 months
- Children without wheezing were enrolled as controls
- Nasal secretions evaluated for viral pathogens by cultures, PCR tests, and antigen detection
- Total IgE and specific IgE antibody

RAL INFECTIONS IN RELATION TO AGE, ATOPY, AND SEASON O ADMISSION AMONG CHILDREN HOSPITALIZED FOR WHEEZING

Heymann JACI 2004; 114: 239

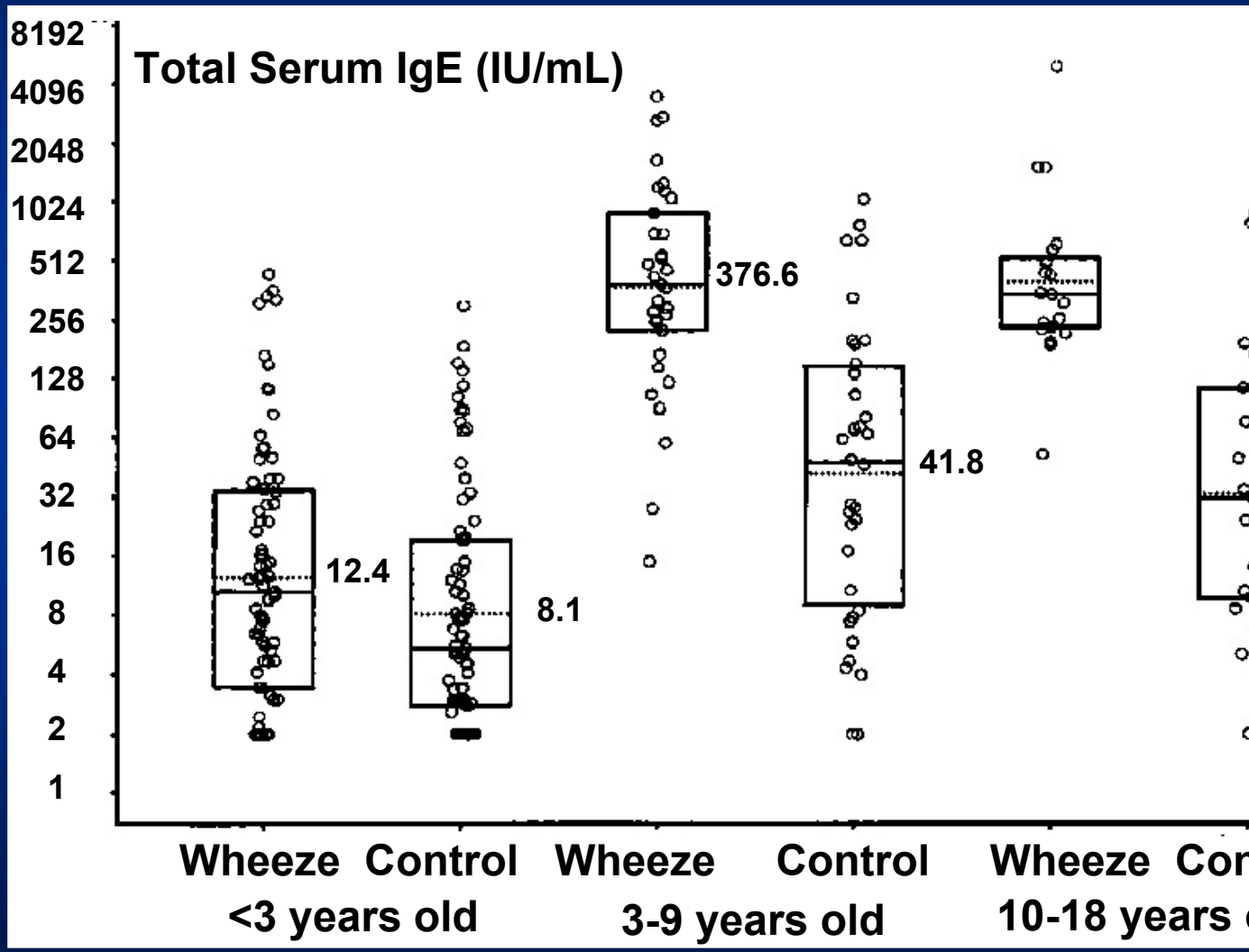


RAL INFECTIONS IN RELATION TO AGE, ATOPY, AND SEASON O ADMISSION AMONG CHILDREN HOSPITALIZED FOR WHEEZING

Heymann JACI 2004; 114: 239

l infections were
ominant risk factor
heezing among
en hospitalized
e 3 yrs of age.
omparison, a large
ity of the wheezing
en age 3 to 18
had striking atopic
cteristics that may
tical as a risk factor
spitalization and
verse response
al infections.

tization and
ure to
llergens may be a
sposing risk factor
augmented
nse to acute
ons with rhinovirus



HRV in infants with asthmalike symptoms and airway function

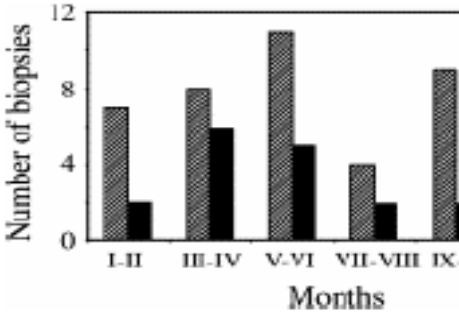
Malmström et al JACI 2006

Objective: To evaluated the presence of HRV in infants (3-26 mo) with recurrent asthmalike respiratory symptoms (recurrent respiratory symptoms for ≥4 wk within the preceding 2 mo).

Method: Body plethysmography (n=201), bronchoscopy (n=68), bronchial biopsies (n=59) for HRV detection.

Results: HRV+ 21/47 (45%) specimens. Abnormal lung function (decreased airways conductance) 18/21 (86%) HRV+ infants vs. 15/26 (58%) HRV− infants (p=0.037). Occurrence of a respiratory infection in the 6 wk preceding bronchoscopy correlated with HRV positivity (p=0.036).

Conclusion: HRV is **frequently found** in the lower airways in infants with recurrent respiratory symptoms, and the majority of these HRV+ infants also showed **increased airway resistance.**



COAST study design

1 parent with
lergy and/or
asthma

Nasal wash → Virology
Wheezing

Sick Visits

New nasal wa
every 2 weeks
symptoms pers

Birth
n=287

2

4

6

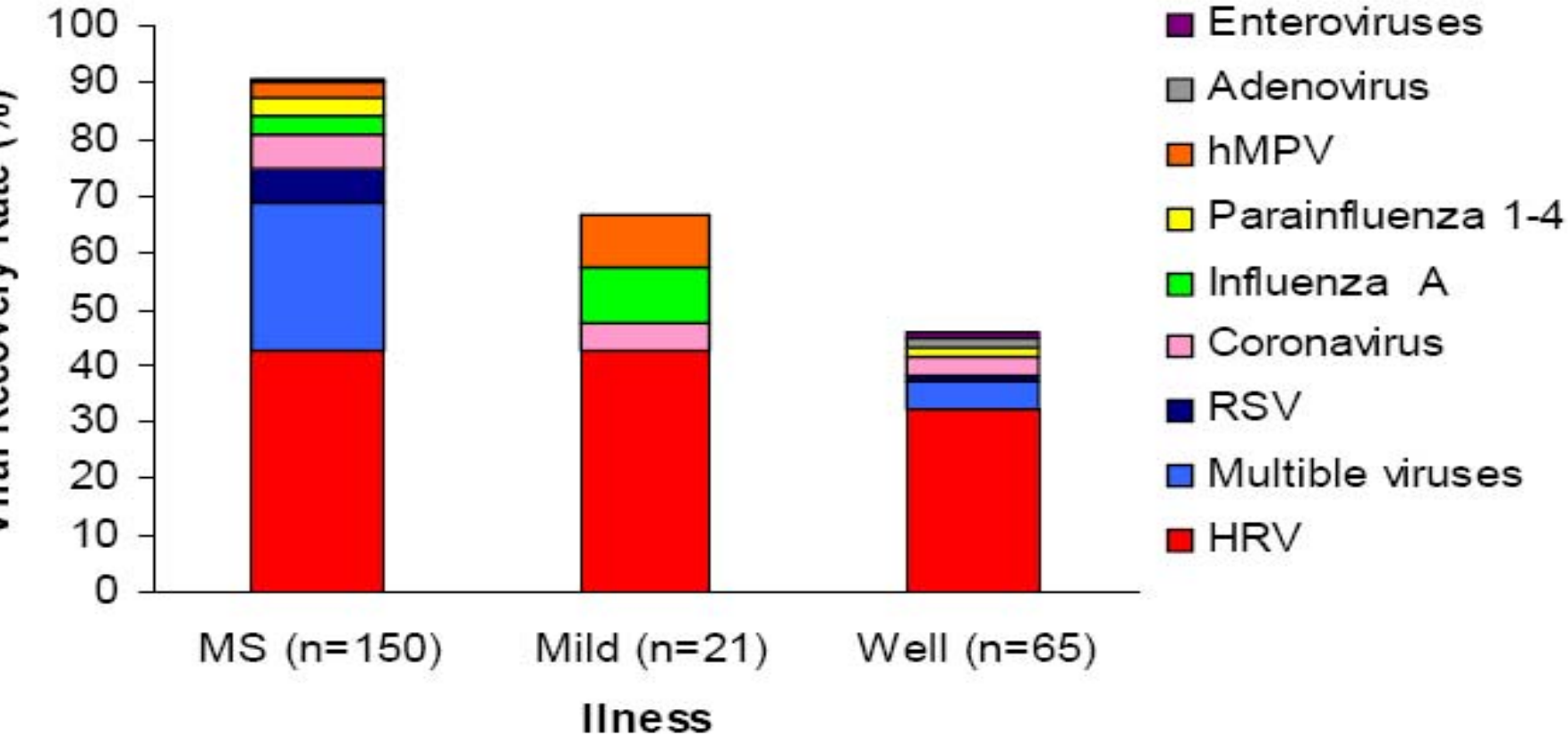
9

One
Year
n=285

Well Visits

Nasal wash → Virology

uses and >160 serotypes tested (not HBoV and HKU1)
ovirus (HRV) was most commonly detected in all visits.
ral, mixed viral and RV findings were linked with severity of illne
4 double RV infections were found.



findings in the 236 study samples of 27 frequently (≥5) ill infants.

Wheezing was closely associated with rhinovirus infection

23 / 27 infants who wheezed had wheezed **at least once** with viral infection

- **78% with rhinovirus**
- **70% with RSV**
- ≤ 39% with other viruses

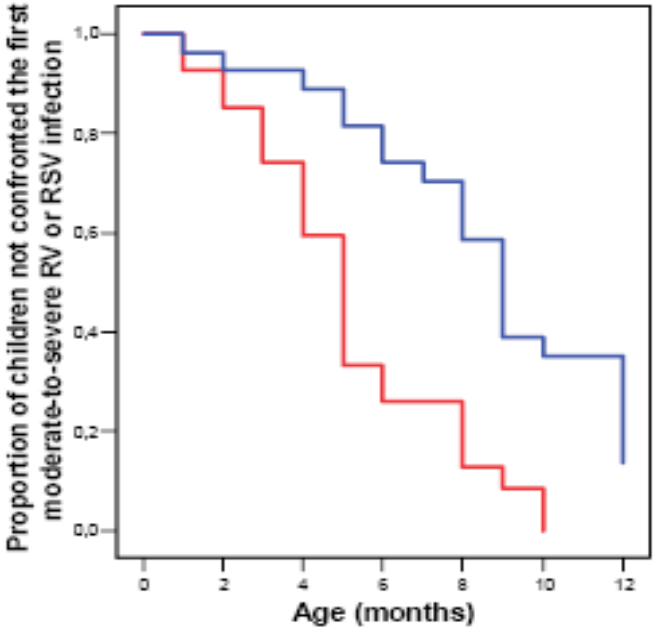
88% of the 68 wheezing **episodes** were associated with viral infection

- **47% with rhinovirus**
- **24% with RSV**
- ≤ 13% with others

Clinical impact of mod-to-sev rhinovirus infections compared to other viruses during the first year of life

hinovirus infections:

- occurred **earliest** (mean age at first infection was 4 months vs. ≥6 months for other viruses, before first RSV infections in 73% of cases)
- were **most frequent** (mean 3.6 vs. <1.0 MSIs for other viruses)
- had **similar severity** compared to RSV (mean [SEM] symptom score, rhinovirus 8.5 [0.8] vs. RSV 9.0 [1.0]



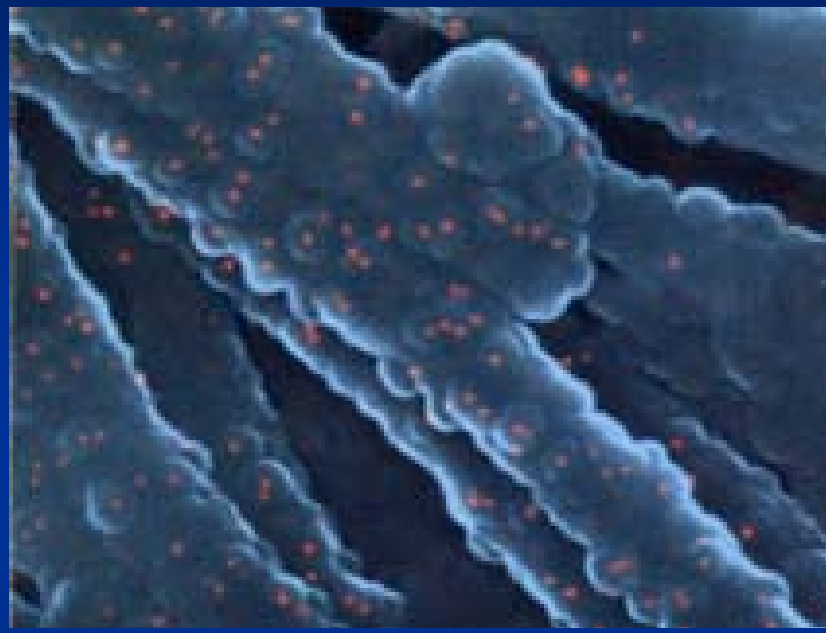
inovirus and the lower respiratory tract

layden - Rev. Med. Virol. 2004; 14: 17–31

- Clinical studies report that RV infection is the second most frequently recognised agent associated with pneumonia and bronchiolitis in infants and young children and commonly causes exacerbations of pre-existing airways disease in older children with asthma.
- RV infection is associated with 1/3 to 1/2 of asthma exacerbations depending on age and is linked to asthma hospitalisations in both adults and children.

IUMAN METAPNEUMOVIRUS

hMPV) was first isolated in the letherlands, in June 2001, from asopharyngeal aspirates of 28 hildren with respiratory tract nfections (van den Hoogen et al. 001). The clinical manifestations of MPV infection in young children are ndistinguishable from the clinical nanifestations of RSV infection

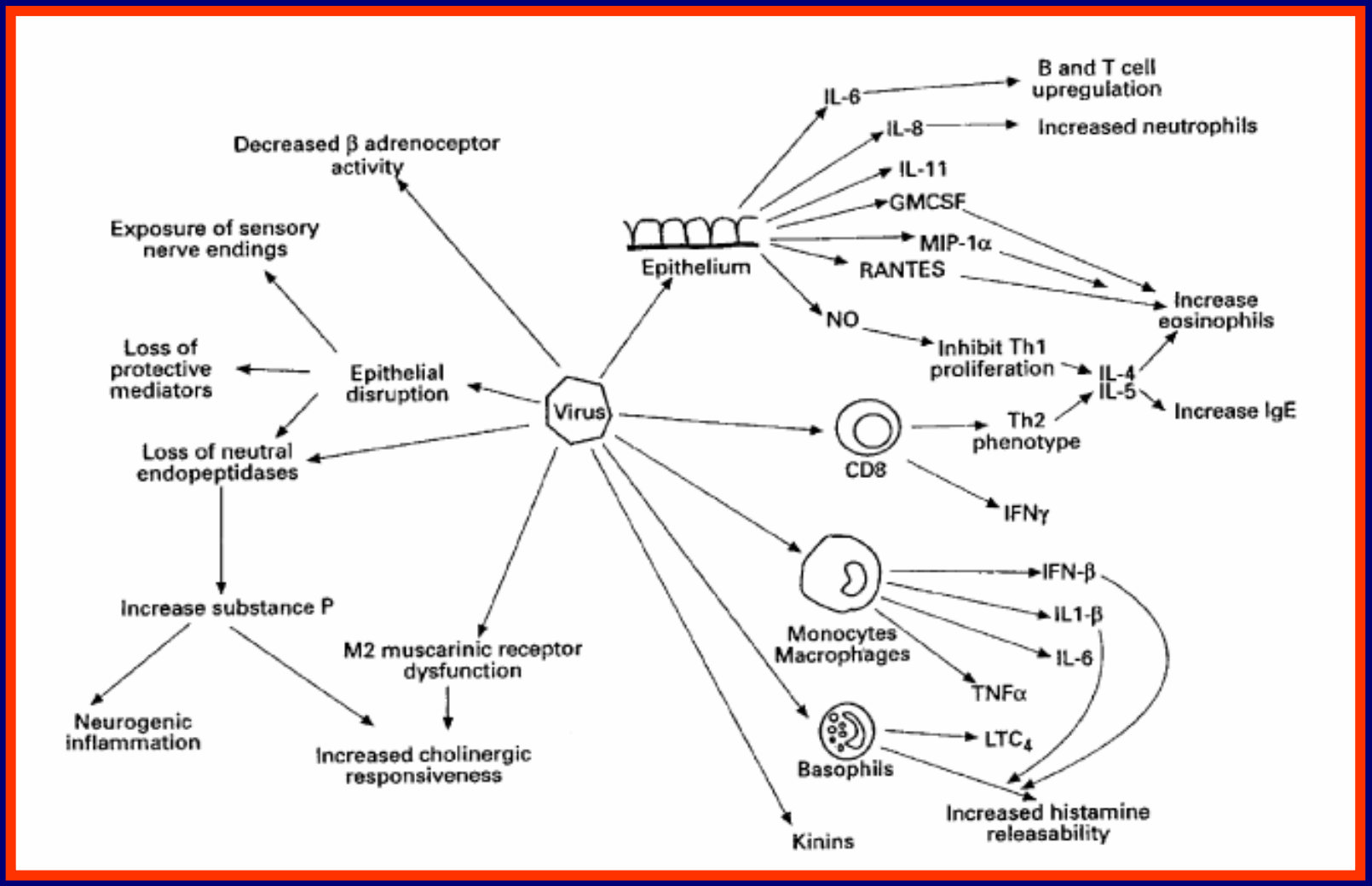


Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. ***García-García ML et al. Pediatr Pulmonol. 2007 May;42(5):458-64***

In 55 children (23 hMPV and 32 RSV acute bronchiolitis) aged 3-5 years and hospitalized, asthma was significantly more frequent in children with hMPV-bronchioliti

irus infections, wheeze and asthma

l Wilson – Paediatric Respiratory Reviews 2003; 4: 184–192



ibra

ttori in grado di indurre
cutizzazioni asmatiche

nfezioni delle vie respiratorie

- Virus (RV,RS, metapneumovirus)
- Germi atipici (Micoplasma pn., Clamidia pn.)

llergeni

nquinanti atmosferici interni (fumo, ecc..)

ed esterni (urbani, industriali, ecc..)

Esercizio fisico

Fattori meteorologici

Farmaci

Alimenti

Ruolo della chlamydia pneumoniae

- Capacità del batterio di crescere e moltiplicarsi in cellule epiteliali della mucosa, macrofagi alveolari cellule muscolari lisce e cellule endoteliali
- Effetto ciliostatico
- Capacità di indurre la sintesi e il rilascio di citochin proinfiammatorie da parte di cellule mononucleat periferiche e dei macrofagi alveolari
- Stretta correlazione tra severità dell'asma ed elevat livelli anticorpali anti-chlamydia pneumoniae

L. C. von Hertzen, EurRespir J 2

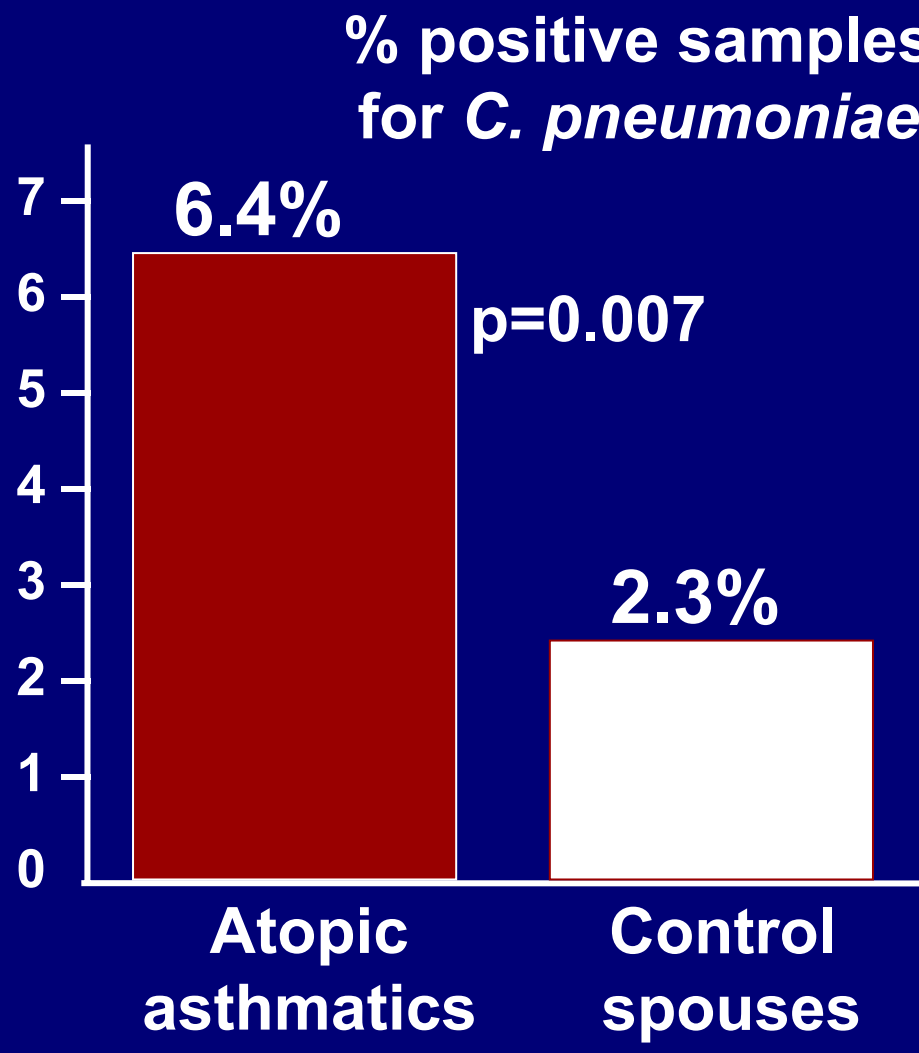
NCREASED FREQUENCY OF DETECTION OF *CHLAMYDOPHILA NEUMONIAE* IN ASTHMA

Biscione et al. Eur. Respir. J. 2004; 24: 745

74 spouse pairs, consisting of one atopic asthmatic and one nonatopic nonasthmatic

Nasal secretions were sampled every 2 weeks from October to December and actively replicating *C. pneumoniae* infection was detected by specific PCR

Chlamydophila pneumoniae infection is detected more frequently among asthmatic participants than normal control participants



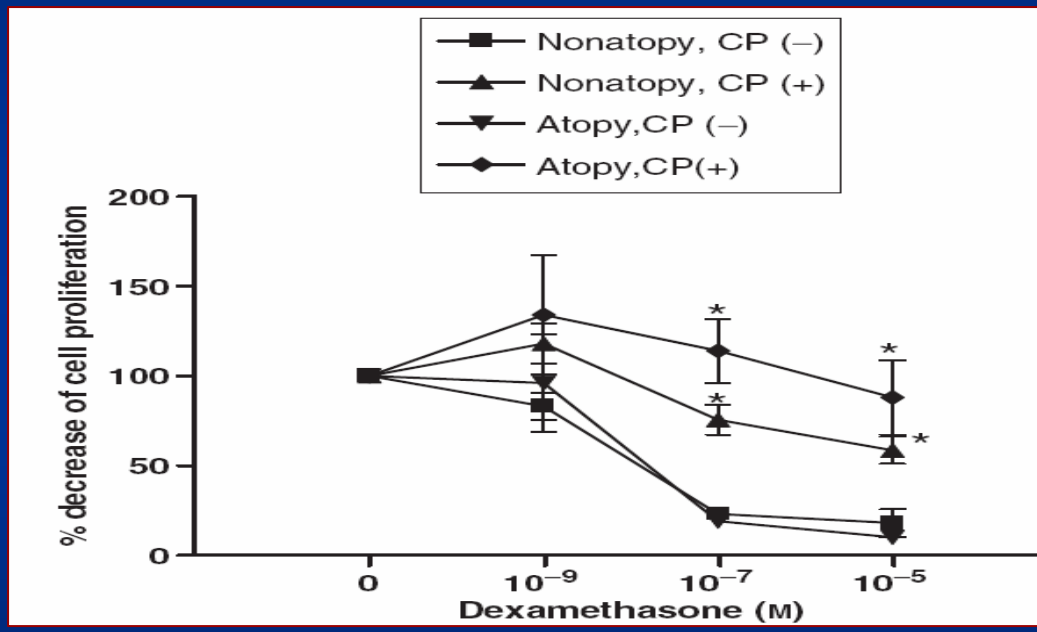
lamydia pneumoniae infection enhances cellular proliferation and reduces stero responsiveness of human peripheral blood mononuclear cells via a tumor necrosis factor-α-dependent pathway

Cho YS et al. - Clinical and Experimental Allergy, 35:1625–1631

han peripheral blood mononuclear (PBMCs) were cultured in vitro in esence or absence of C. moniae infection.

ults Cellular proliferation was icantly higher in C. pneumoniae-ed PBMCs than in uninfected Cs, which is more prominent in Th2-nant microenvironment.

ntiproliferative and pro-apoptotic of corticosteroid were icantly reduced in C. moniae infected PBMCs ared with uninfected PBMCs



C. pneumoniae infection enhanced the proliferation and survival of immune and inflammatory cells, resulting in steroid resistance

Pneumoniae and wheezing

In childhood, C. pneumoniae infection may induce wheezing, which can persist, even after a systemic and/or inhalatory steroid therapy, until the infection has been completely treated

Block S. et al. - Pediatr. Infect. Dis. 1995;14,471
Esposito S. et al. - Eur. Resp. J. 2000;16, 1142
Schmidt MN. et al - P.A.I. 2001;12, 257
Kutlin S. et al. - Antimicrob. Ag. Chemiother. 2002;46,409
Lewanske jr RF – CHEST 2003;123:385s-390s

Infezione da mycoplasma pneumoniae

↓

Formazione bronchiale di un infiltrato di neutrofili

↓

Maggiore produzione di IL-4, IL-5, TNFα
Minore produzione di IFN-γ , Th1

↓

Iperreattività bronchiale e asma

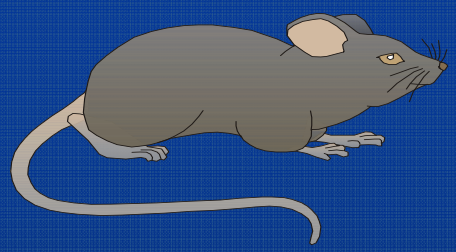
Montalbano MM.,Curr Opin Pediatr

giogenesis and Remodeling of Airway Vasculature in onic Inflammation

c Donald - AJRCCM 2001; 164: S39-45

MYCOPLASMA INFECTION MODEL OF CHRONIC AIRWAY INFLAMMATION

inoculated intranasally with M. pneumoniae



the microvasculature of the airway mucosa begins to change soon after infection

angiogenesis and microvascular remodeling become long-lasting features of the disease

okine Secretion in Children With Acute Mycoplasma eumoniae Infection and Wheeze

posito et al - Pediatric Pulmonology 2002;34:122–127

- *The children with acute M. pneumoniae infection and wheeze had higher IL-5 concentrations than those with asymptomatic acute infection and without wheeze (P<0.0001).*
- *No significant between-group differences were observed in terms of IL-2, IFN-γ, or IL-4 levels.*

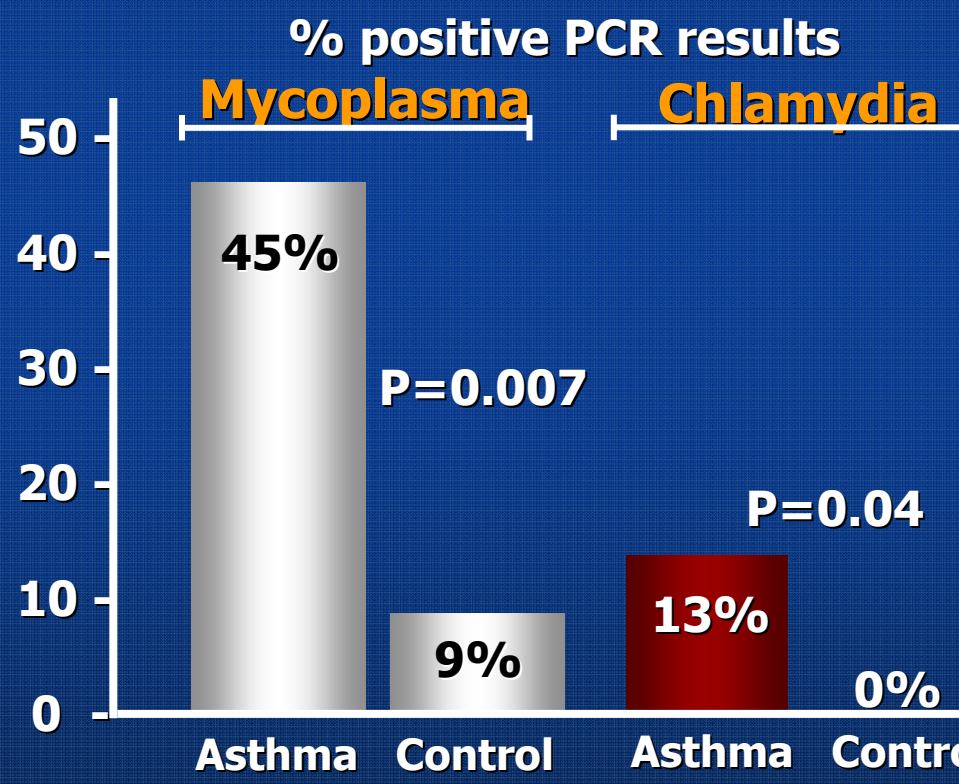
- *IL-5 seems to be essenti for the development of hyperresponsiveness.*
- *IL-5 can therefore cause high level of local inflammation that may cause considerable local damage to host tissues.*

Schwarze J et al. - J Immunol 199
AJRCCM 200

nk between chronic asthma and chronic infection

in - JACI 2001; 107: 595

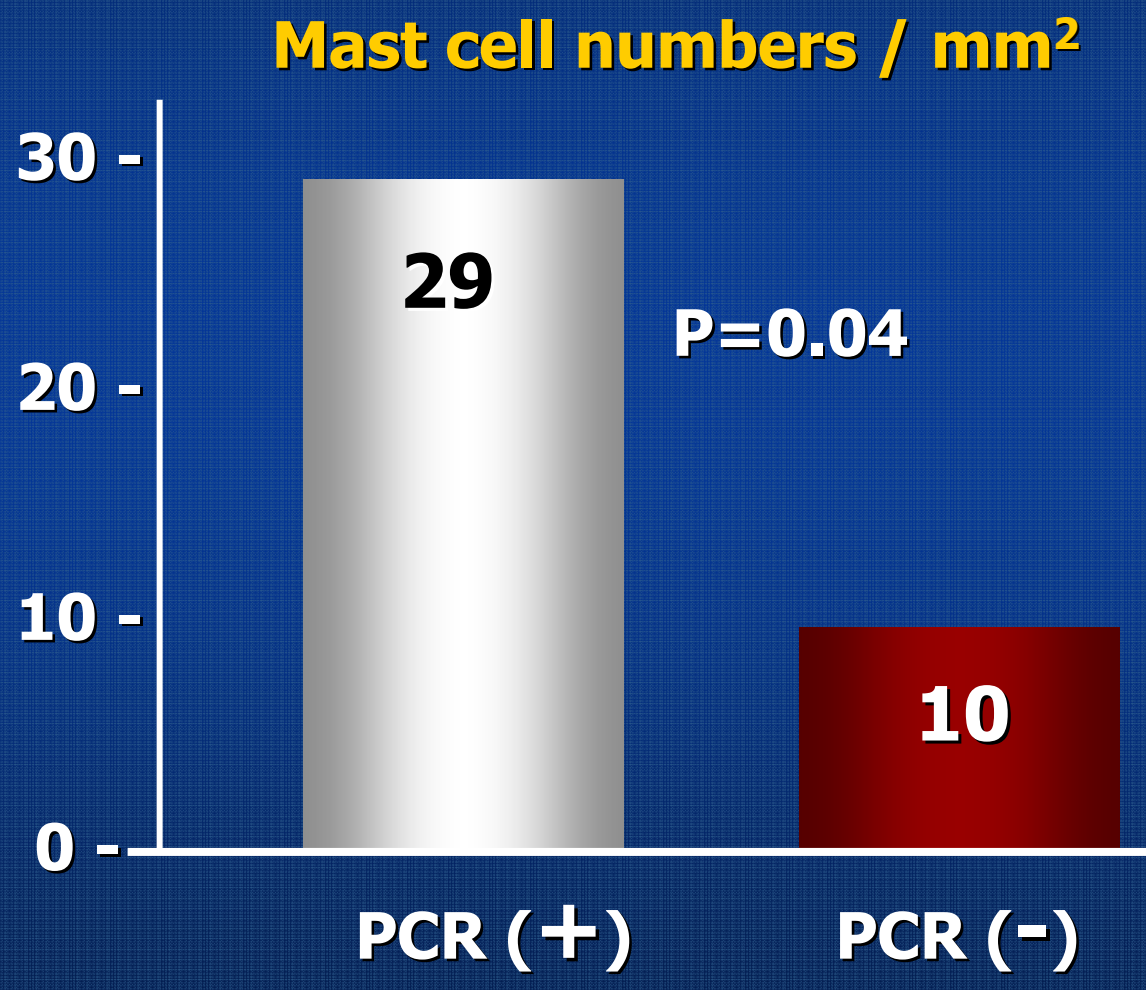
This study on the relationship of M. pneumoniae and C. Pneumoniae in patients with chronic stable asthma gives further insight into the possible link between chronic infection and chronic asthma.



nk between chronic asthma and chronic infection

in - JACI 2001; 107: 595

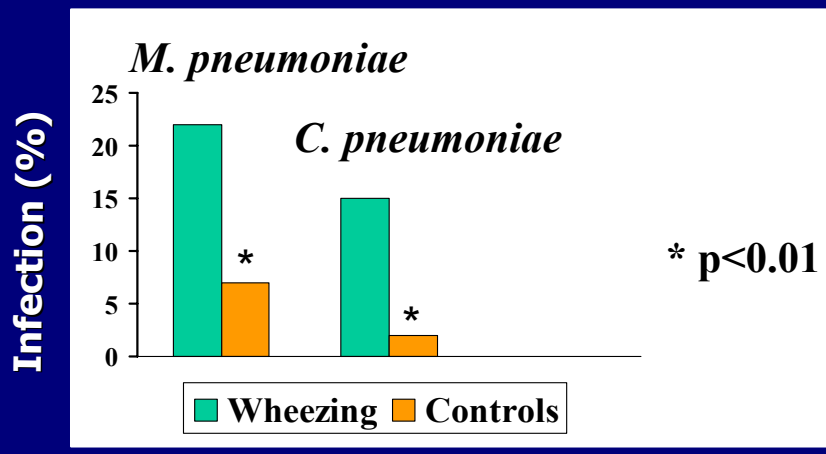
The increased number of tissue mast cell in the group with PCR (+) results suggests a potential interaction between infection and allergen sensitization.

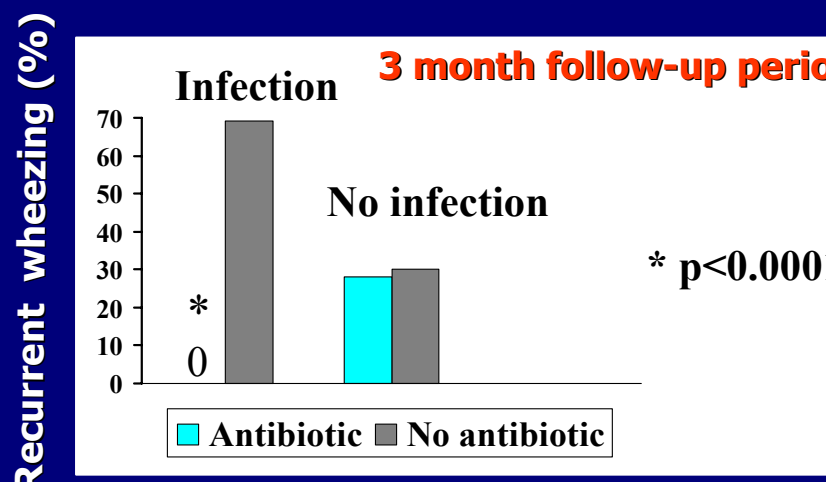


portance of acute *Mycoplasma pneumoniae* and *Chlamydia umoniae* infections in children with wheezing

posito - Eur Respir J 2000;16:1142

- ***M. pneumoniae*** **and** ***C. pneumoniae*** **are significantly related to wheezing in children particularly in those with recurrent episodes**
- **Clarithromycin may improve the course of wheezing in patients with acut infection**





ct of clarithromycin on cytokines and chemokines in children with an acute
erbation of recurrent wheezing: a doubleblind,randomized, placebo-controlled t
ca-Aten M et al. - Ann Allergy Asthma Immunol. 2006;97:457–463

Children with a history of recurrent wheezing or asthma and who presented
h an acute exacerbation of wheezing

coplasma pneumoniae and *Chlamydophila pneumoniae* infection were

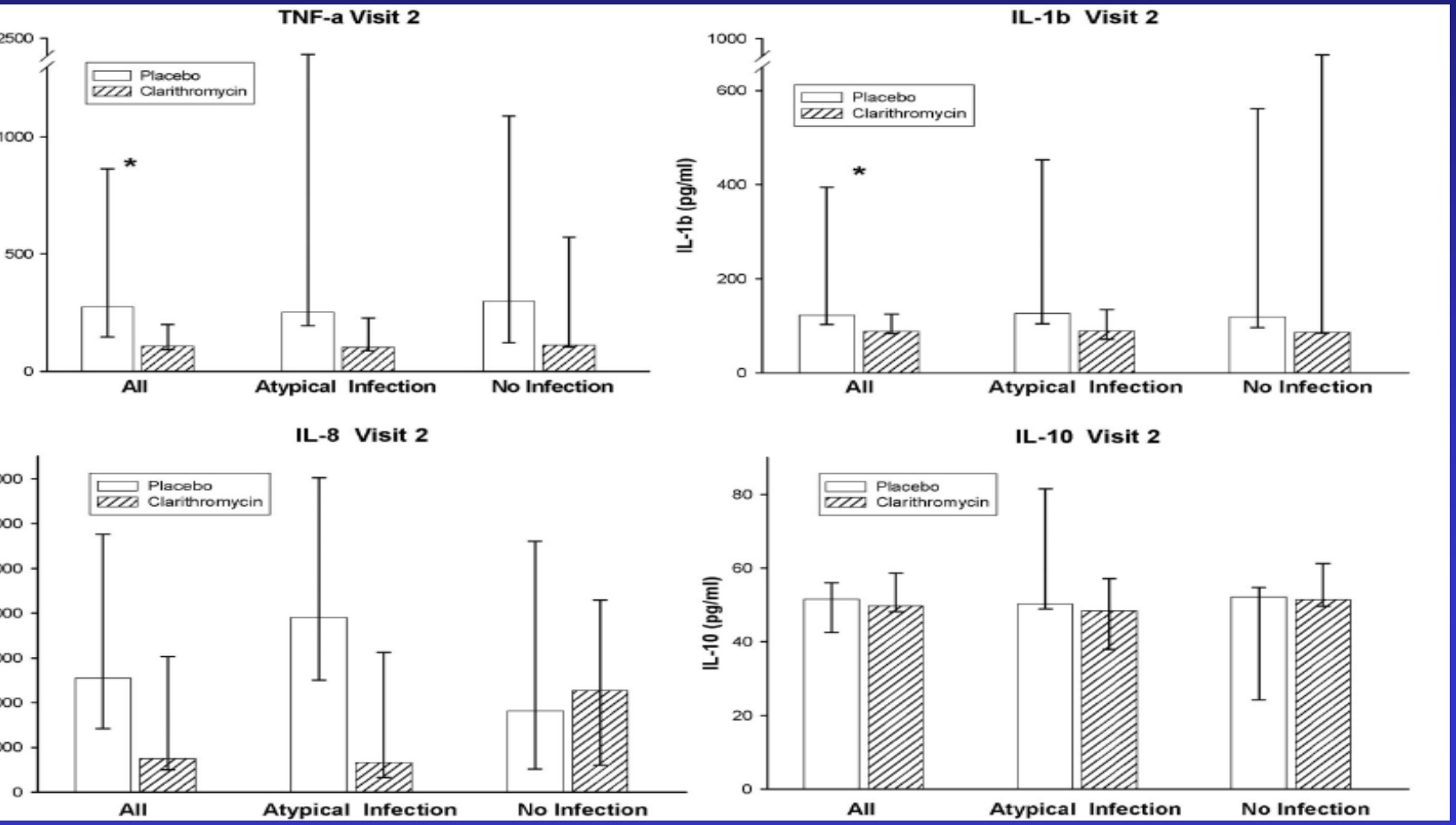
larithromycin therapy reduces mucosal TNF-α, IL-1ß, and IL
10 concentrations in children with an acute exacerbation of
recurrent wheezing

acrophage inflammatory protein 1, and monocyte chemoattractant protein 1
re measured in serum and/or nasopharyngeal aspirates before, during, and
er therapy

sopharyngeal concentrations of TNF-, IL-1, and IL-10 were significantly and
sistently lower in children treated with clarithromycin compared with
cebo

Effect of clarithromycin on cytokines and chemokines in children with an acute exacerbation of recurrent wheezing: a doubleblind,randomized, placebo-controlled tria

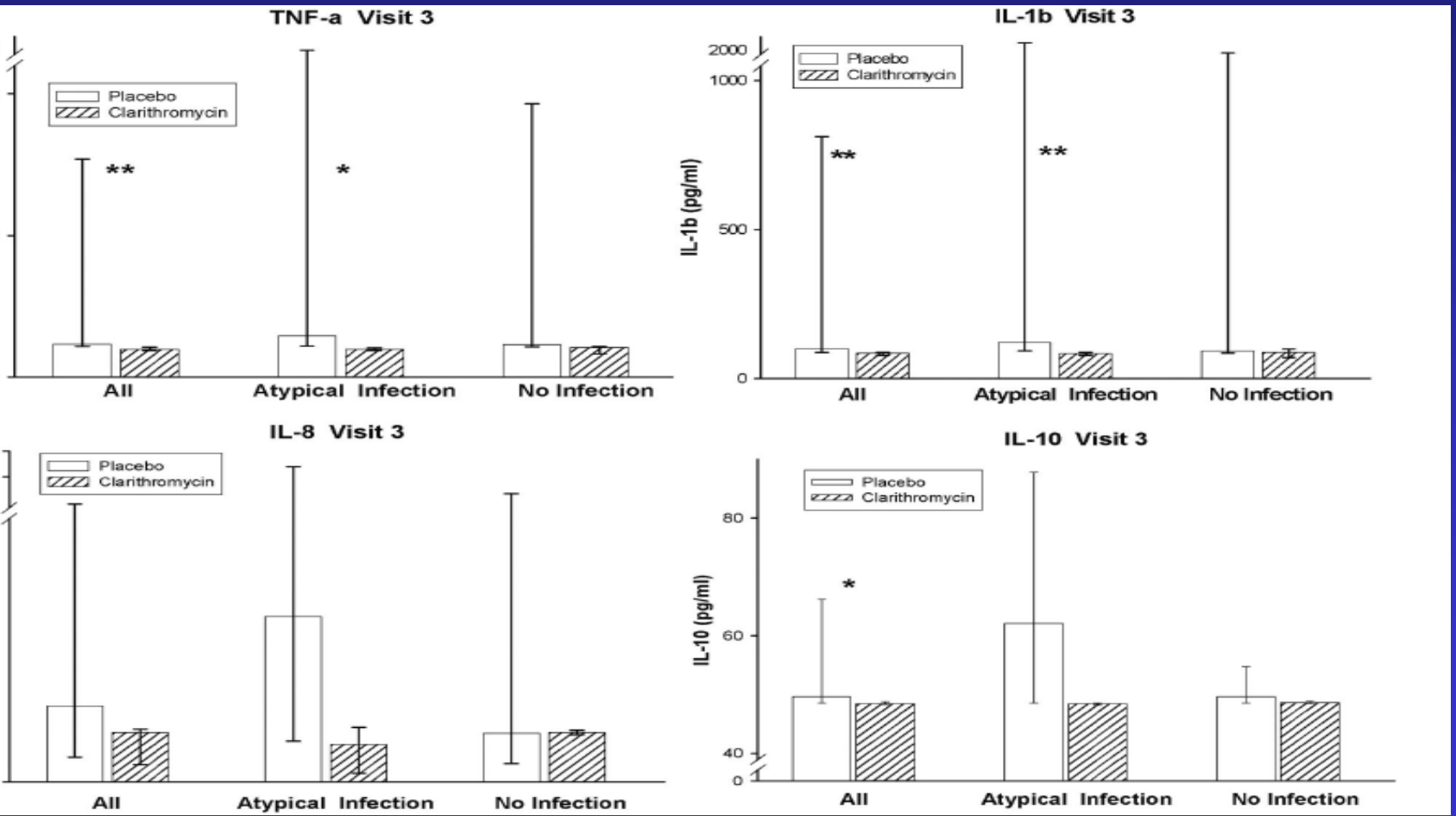
Fonseca-Aten M et al. - Ann Allergy Asthma Immunol. 2006;97:457–463



*p<0

Effect of clarithromycin on cytokines and chemokines in children with an acute exacerbation of recurrent wheezing: a doubleblind,randomized, placebo-controlled tria

Fonseca-Aten M et al. - Ann Allergy Asthma Immunol. 2006;97:457–463



*p<0

fetto antinfiammatorio dei macrolidi

- Agiscono sulla funzione dei neutrofili (ne riducono numero e attività)
- Riducono il livello di citochine quali IL-1β , IL-6 e IL8 (chemiotattica per eosinofili e neutrofili)
- Riducono il reclutamento degli eosinofili nelle vie aeree
- Sopprimono la produzione di TNF-α e GM-CSF
- Inibiscono la generazione dei superossidi ed elastasi da parte dei granulociti attivati
- Accelerano l'apoptosi dei neutrofili
- Riducono la broncocostrizione inibendo le risposte colinergich a livello delle vie aeree
- Inducono una riduzione nella secrezione di muco da parte dell globets cells delle vie aeree

Grazie

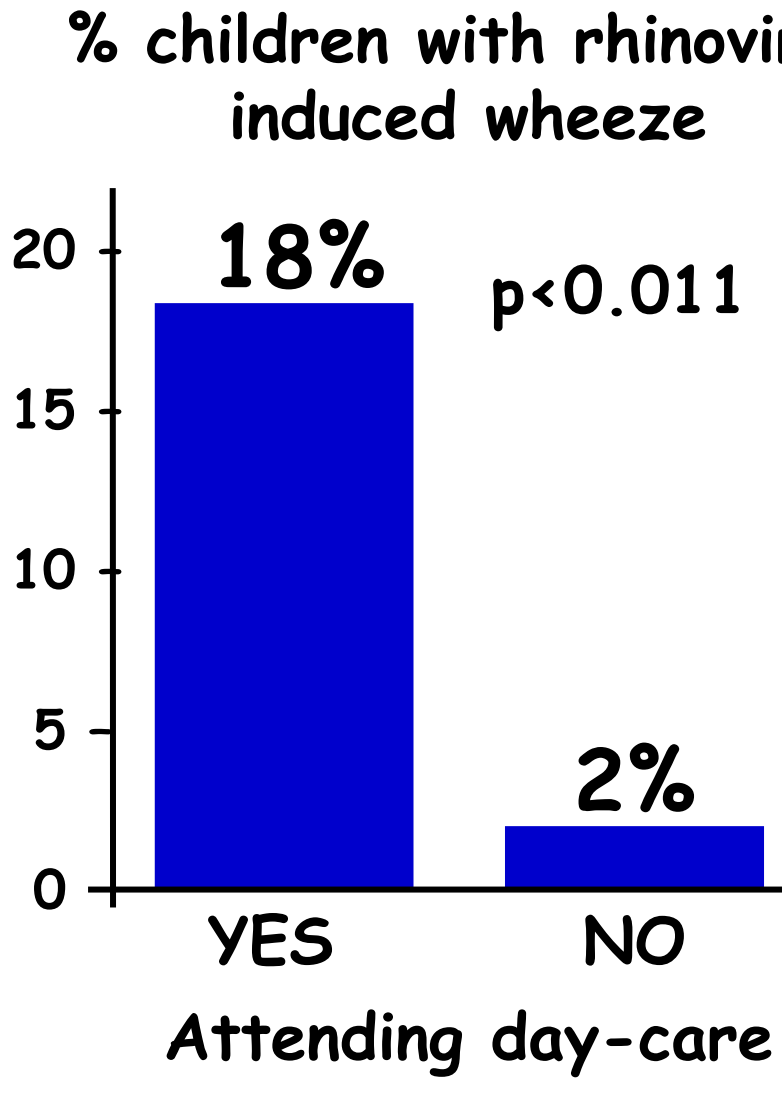
CYTOKINE RESPONSE PATTERNS, EXPOSURE TO VIRUSES, AND RESPIRATORY INFECTIONS IN THE FIRST YEAR OF LI

Copenhaver AJRCCM 2004; 170: 175

285 children were enrolled n the Childhood Origins of Asthma Project at birth and followed for at east 1 year

Cord blood and 1-year mononuclear cells were stimulated with phytohemagglutinin

Cytokine-response profiles were measured by enzyme-linked mmunosorbent assay

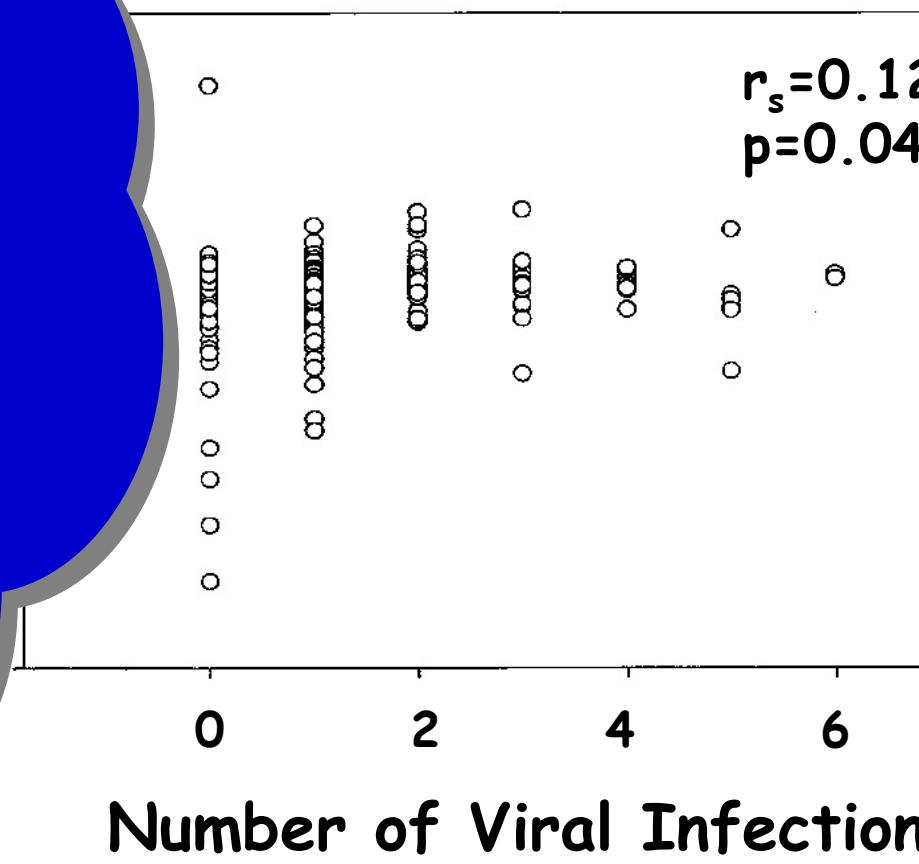


CYTOKINE RESPONSE PATTERNS, EXPOSURE TO VIRUSES, AND RESPIRATORY INFECTIONS IN THE FIRST YEAR OF LIFE

CM 2004; 170: 175

35

The interval change in infantile IFN-γ responses correlated positively with the frequency of viral infections in infancy. The frequency of viral infections in infancy can influence IFN-γ responses.



rot

y enz

mmunosorbent

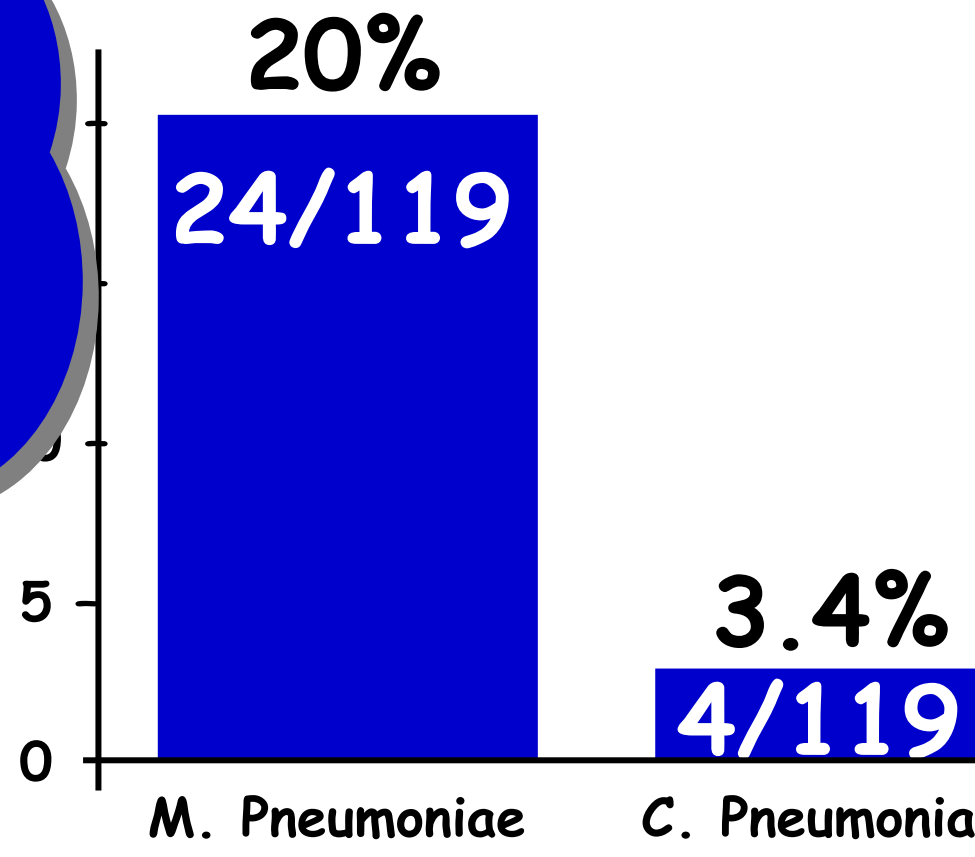
YCOPLASMA PNEUMONIAE AND ASTHMA IN CHILDREN

Biscardi Clin. Infect. Dis. 2004; 38: 1341

M. Pneumoniae may play a role in the onset of asthma in predisposed children and could be a trigger for recurrent wheezing

ch onde

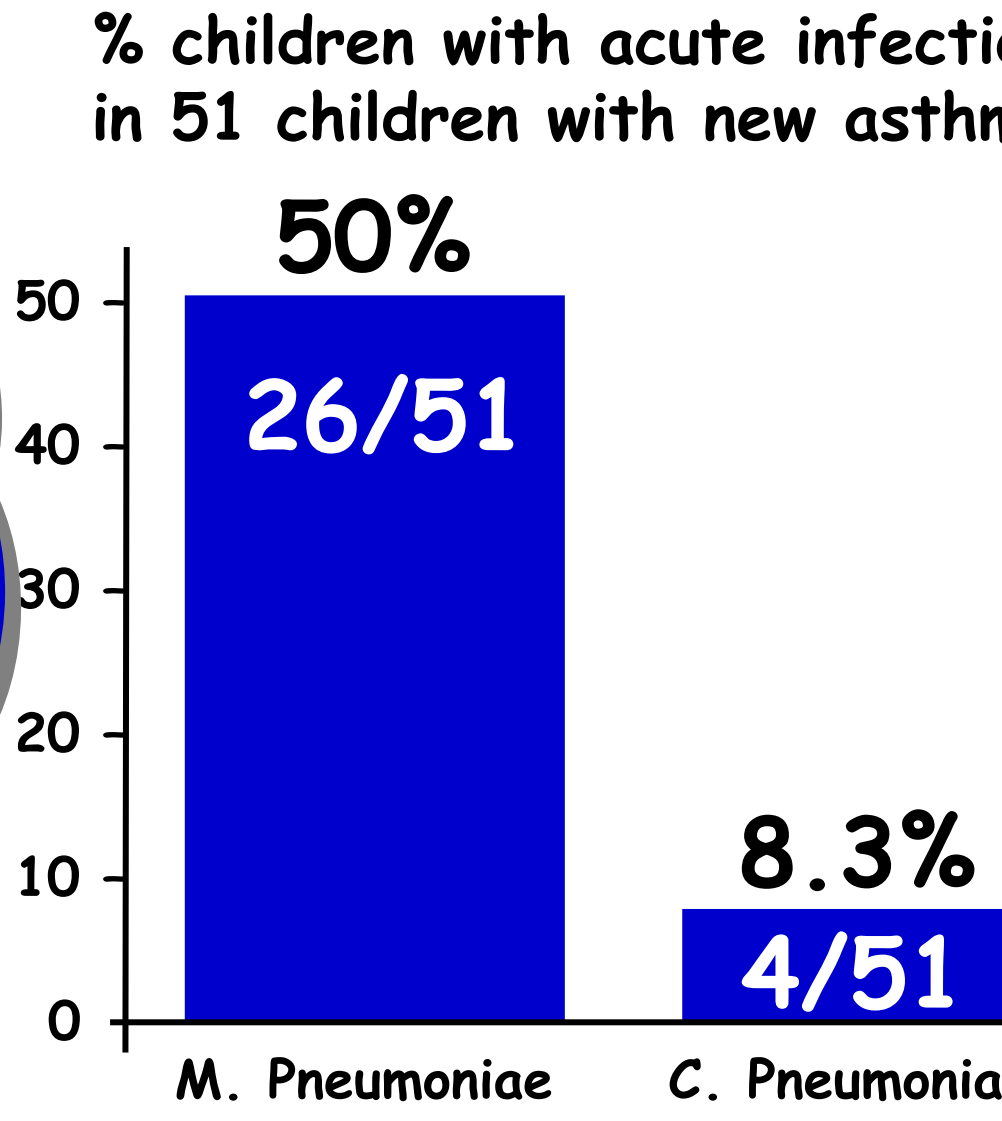
% children with acute infecti
in 119 children with previous
diagnosed asthma



YCOPLASMA PNEUMONIAE AND ASTHMA IN CHILDRE

Biscardi Clin. Infect. Dis. 2004; 38: 1341

Infected children were more likely than non infected children to present recurrence of exhacerbations $p<0.05$



PRIOR *BORDETELLA PERTUSSIS* INFECTION MODULATES ERGEN PRIMING AND THE SEVERITY OF AIRWAY PATHOLO IN A MURINE MODEL OF ALLERGIC ASTHMA.

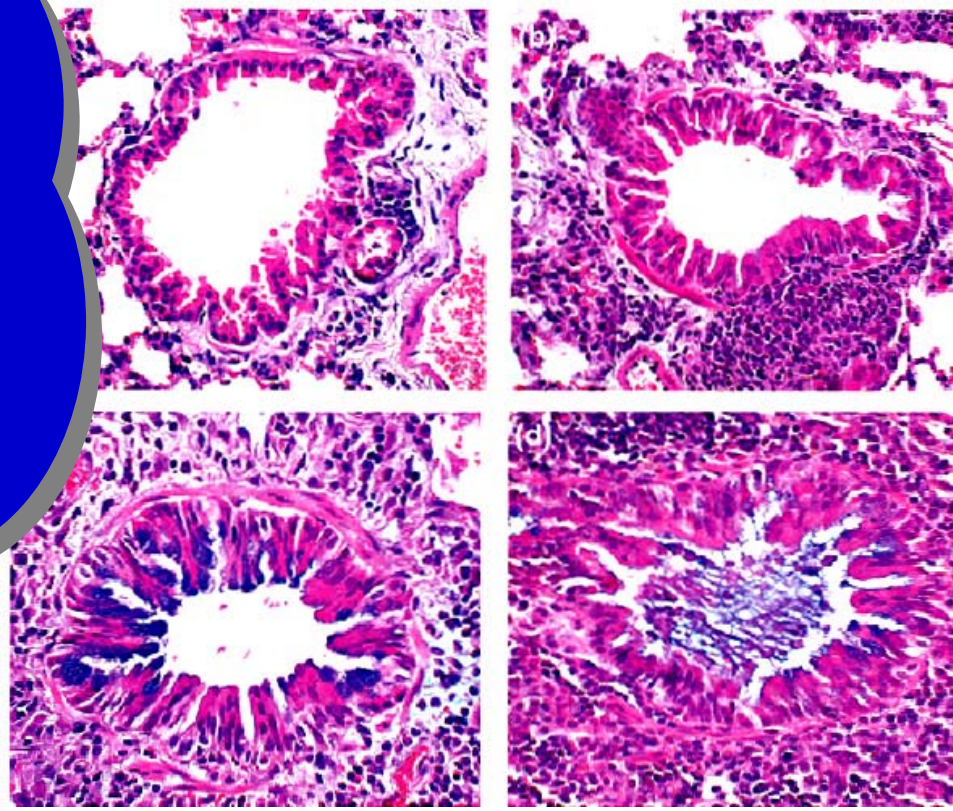
Enn Clin Exp. Allergy 2004; 34: 1488

A Th1 response induced by a common childhood infection does not protect against bronchial hyper-reactivity, but rather exacerbates the allergic asthmatic response, despite modulation of immune mediators.

sensitization

Control

B pertussis only



OVA only

OVA + *B pertussis*

n

l

✓ Increase R

INCREASED FREQUENCY OF DETECTION OF *CHLAMYDOPHILA PNEUMONIAE* IN ASTHMA

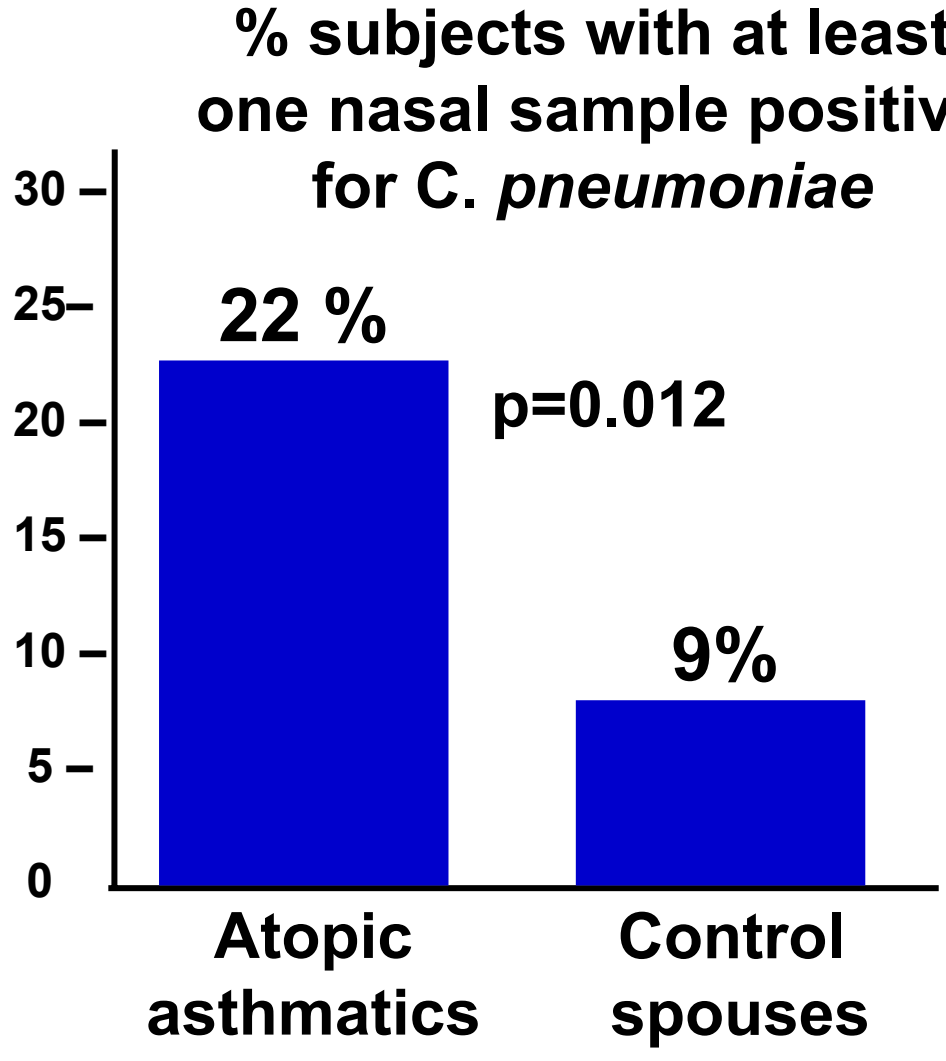
Biscione Eur. Respir. J. 2004; 24: 745

4 spouse pairs

on pic

ssible explanation
he above findings
d be the presence
impaired immune
responses to
C. pneumoniae
ctions in asthma
ficient production
of IFN-γ?)

tion



Neonatal Chlamydial Infection Induces Mixed T-Cell Responses That Drive Allergic Airway Disease

Horvat JC et al. - Am J Respir Crit Care Med 2007; 176:556–564,

Neonatal or adult mice were given a chlamydial infection and 6 weeks later were sensitized and subsequently challenged with ovalbumin.

RESULTS: Neonatal but not adult infection resulted in significant decreases in interleukin-5 production from helper T cells and by the numbers of eosinophils recruited to the lung in response to ovalbumin exposure

Neonatal Chlamydial Infection Induces Mixed T-Cell Responses That Drive Allergic Airway Disease

Horvat JC et al. - Am J Respir Crit Care Med 2007; 176:556–564,

he effects of early-life infection were associated with the eneration of both type 1 and 2 ovalbumin-specific helper T-

Early-life chlamydial infection induces a mixed type 1 nd 2 T-cell response to antigen, which differentially affects t development of key features of AAD in the adult

xacerbated other hallmark features of asthma: mucus ypersecretion and airway hyperresponsiveness

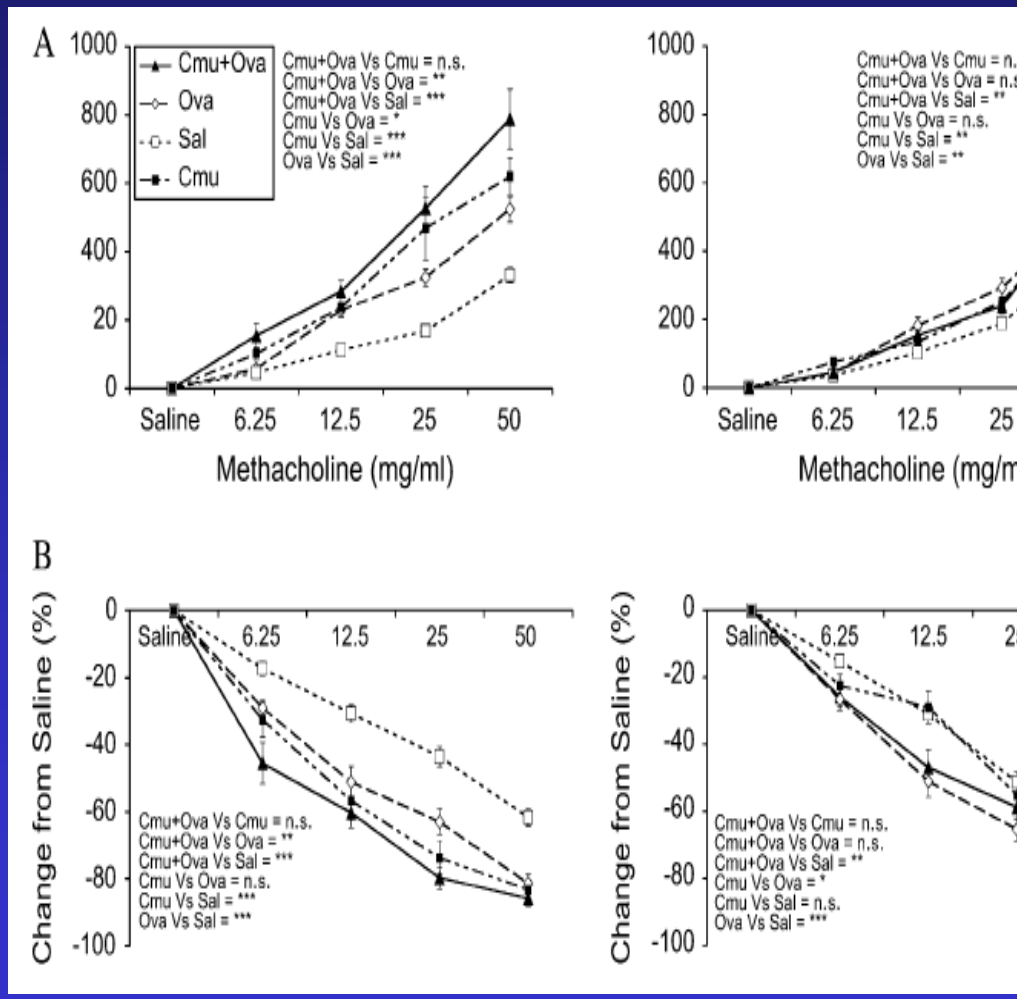
nfection prolonged the expression of AAD and these effects ere restricted to early-life infection

Neonatal Chlamydial Infection Induces Mixed T-Cell Responses That Drive Allergic Airway Disease

Horvat JC et al. - Am J Respir Crit Care Med 2007; 176:556–564,

ay hyperresponsiveness,
ured as airway resistance (A)
dynamic compliance (B), after
muridarum infection and
peritoneal induction of allergic
y disease (Cmu/Ova),
pared with infection (Cmu),
umin (Ova), and
le(saline [Sal]) groups.

< 0.05
< 0.01
< 0, 0.001.
s.: not significant



IFN-γ–induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations

Wark P et al. - J Allergy Clin Immunol 2007;120:586-93

onchial epithelial cells (BECs) were obtained from bronchial
shings of steroid naive asthmatic subjects and healthy nonatopic
trol subjects. Cells were infected with rhinovirus 16. Inflammatory
liators were measured by means of 0 flow cytometry with a
ometric bead array

bjects with acute asthma and virus infection were recruited; they
e characterized clinically by using lung function tests and had
od taken to measure the inflammatory mediators identified as
portant by the BEC experiments

N-γ–induced protein 10 (IP-10) and RANTES were released in the
atest quantities, followed by IL-6, IL-8, and TNF- α

N-γ–induced protein 10 is a novel biomarker rhinovirus-induced asthma exacerbations

Wark P et al. - J Allergy Clin Immunol 2007;120:586-93

kamethasone treatment of BECs only partially suppressed IP-10
TNF- α but was more effective a suppressing RANTES, IL-6, and IL-8.

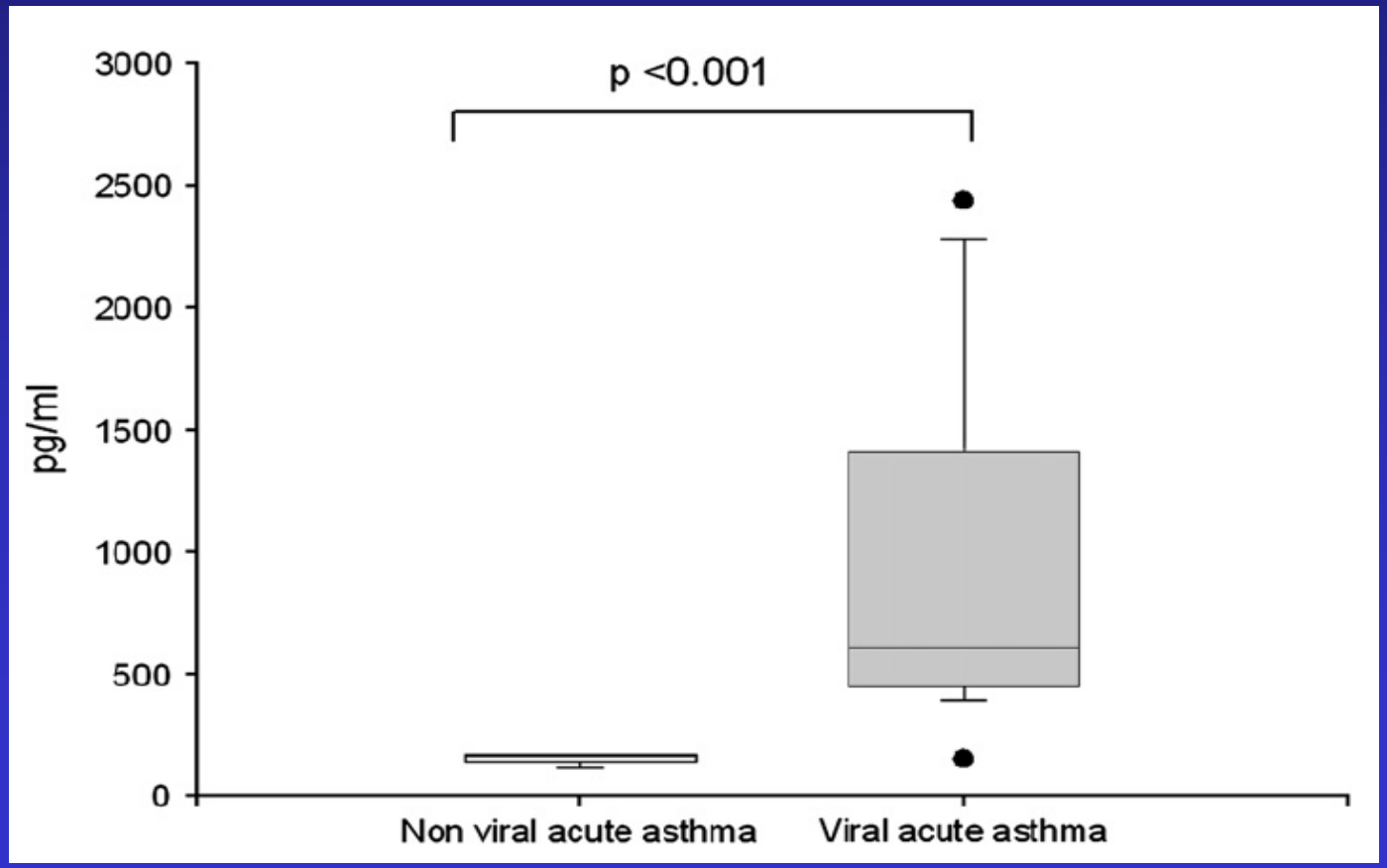
IP-10 release is specific to acute virus-uced asthma; measurement of serum IP could be used to predict a viral trigger to acute asthma

reased serum IP-10 levels were strongly associated with more
ere airflow obstruction (r520.8; p <0 .01).

N-γ–induced protein 10 is a novel biomarker o
rhinovirus-induced asthma exacerbations

Wark P et al. - J Allergy Clin Immunol 2007;120:586-93

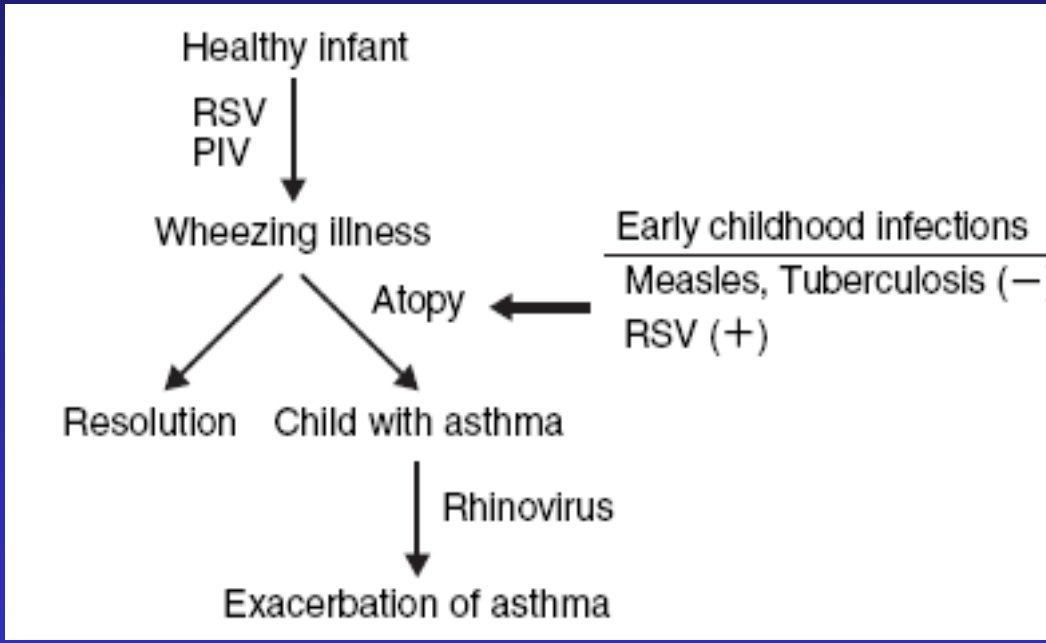
Serum IP-10 levels at presentation with acute asthma



Respiratory Viral Infections and Early Asthma in Childhood

Jae-Won Oh - Allergology International. 2006;55:369-372

ationship of viral
ctions to acute
eezing illnesses
asthma.



RSV: respiratory syncytial virus
PIV: parainfluenza virus
(-) expresses inhibition
(+) expresses stimulation

NTELUKAST AND THE PREVENTION OF VIRAL DUCED ASTHMA (The PREVIA multi-centric study)

isgaard et al. – ERS 2003

The results demonstrate that montelukast significantly reduced t asthma exacerbations, compared to placebo, in 2 to 5 year-old children with history of episodic astmatic symptoms.

This one year treatment was well tolerated.