Agenti biologici nell'asma non eosinofilico

Prof. Francesco Blasi

Department of Pathophysiology and Transplantation, University of Milan, Italy
Head Cardio-Thoracic Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Cà Granda Milan, Italy

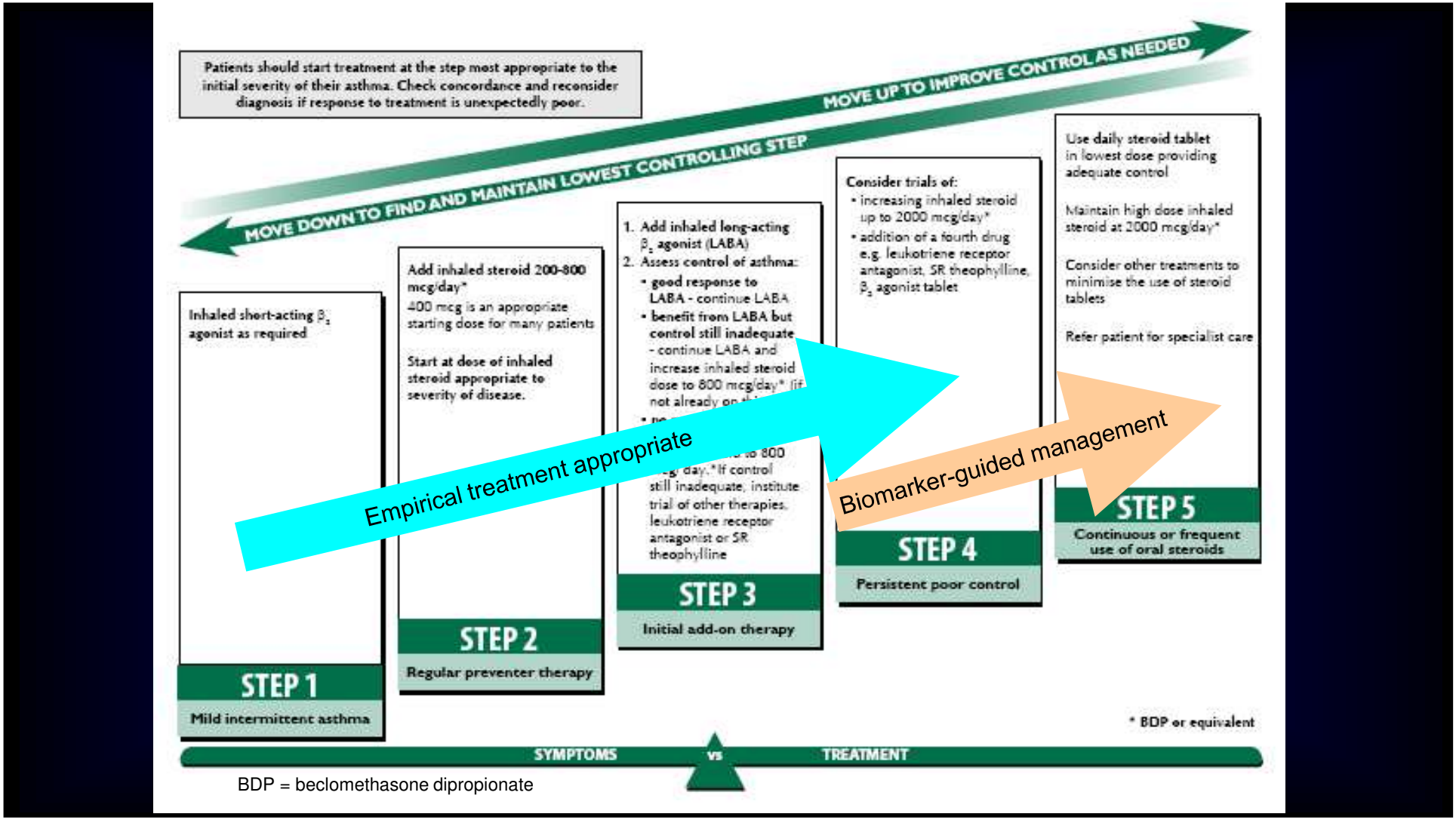
UNIVERSITÀ DEGLI STUDI DI MILANO

ITALIAN RESPIRATORY SOCIETY
SIP
SOCIETÀ ITALIANA DI PNEUMOLOGIA

Disclosures

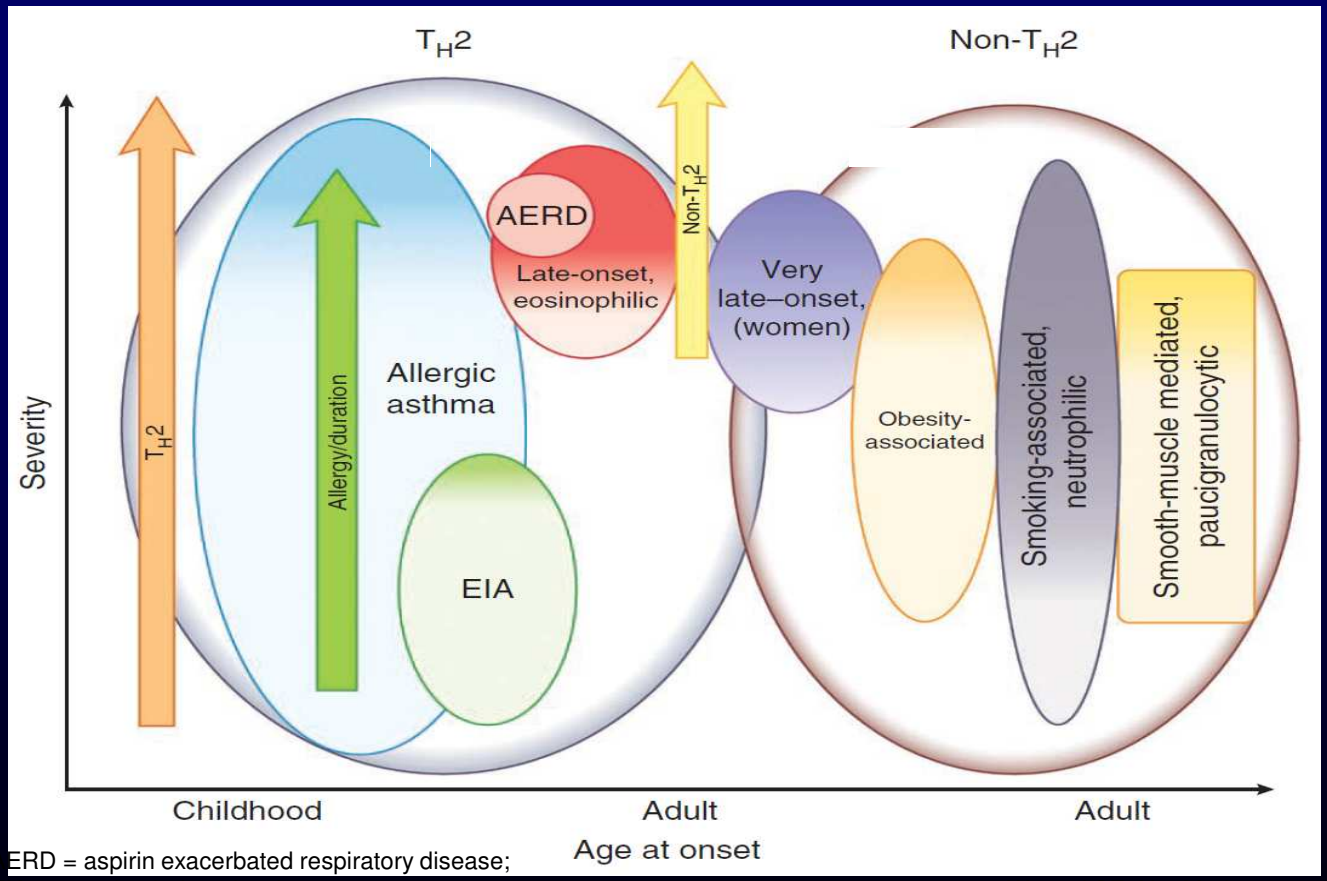
- I have accepted grants, speaking and conference invitations from Angelini, ALK, AstraZeneca, Bayer, Chiesi, Dompè, GSK, Guidotti-Malesci, Menarini, Novartis, Pfizer, Sanofi, Teva, Thermo Fisher and Zambon

- I have had recent or ongoing consultancy with Angelini, AstraZeneca, Chiesi, GSK, Menarini, Novartis, Teva, Zambon



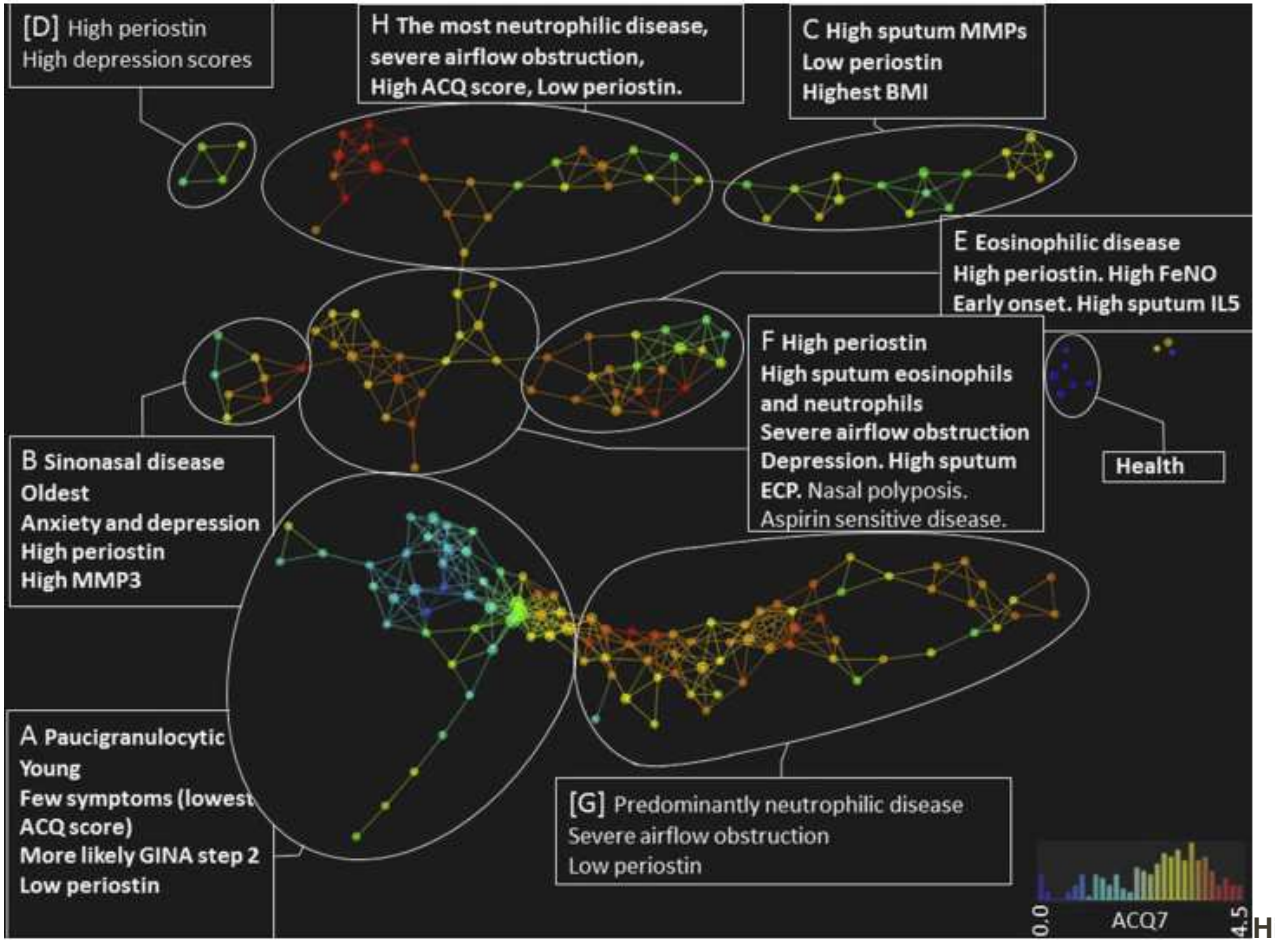
BDP = beclomethasone dipropionate

Asthma phenotypes



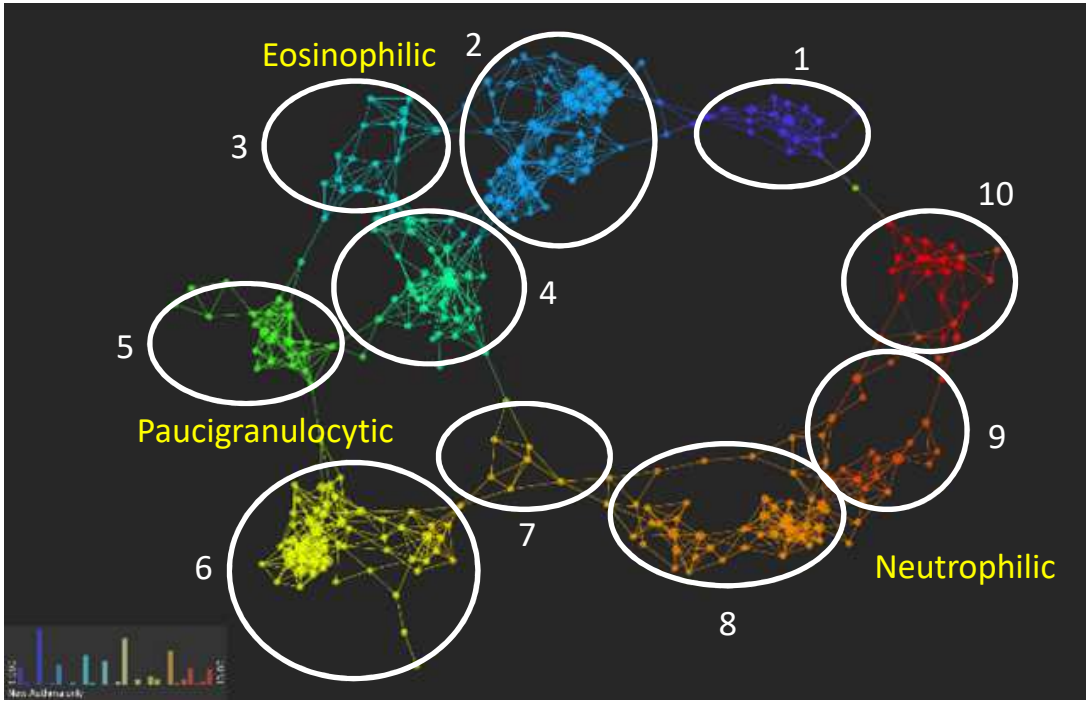
ERD = aspirin exacerbated respiratory disease;

TDA ENDOTYPING IN ASTHMA: TOPOLOGICAL NETWORK in Wessex Severe Asthma Cohort



Hinks et al JACI 2016; 138: 61-75

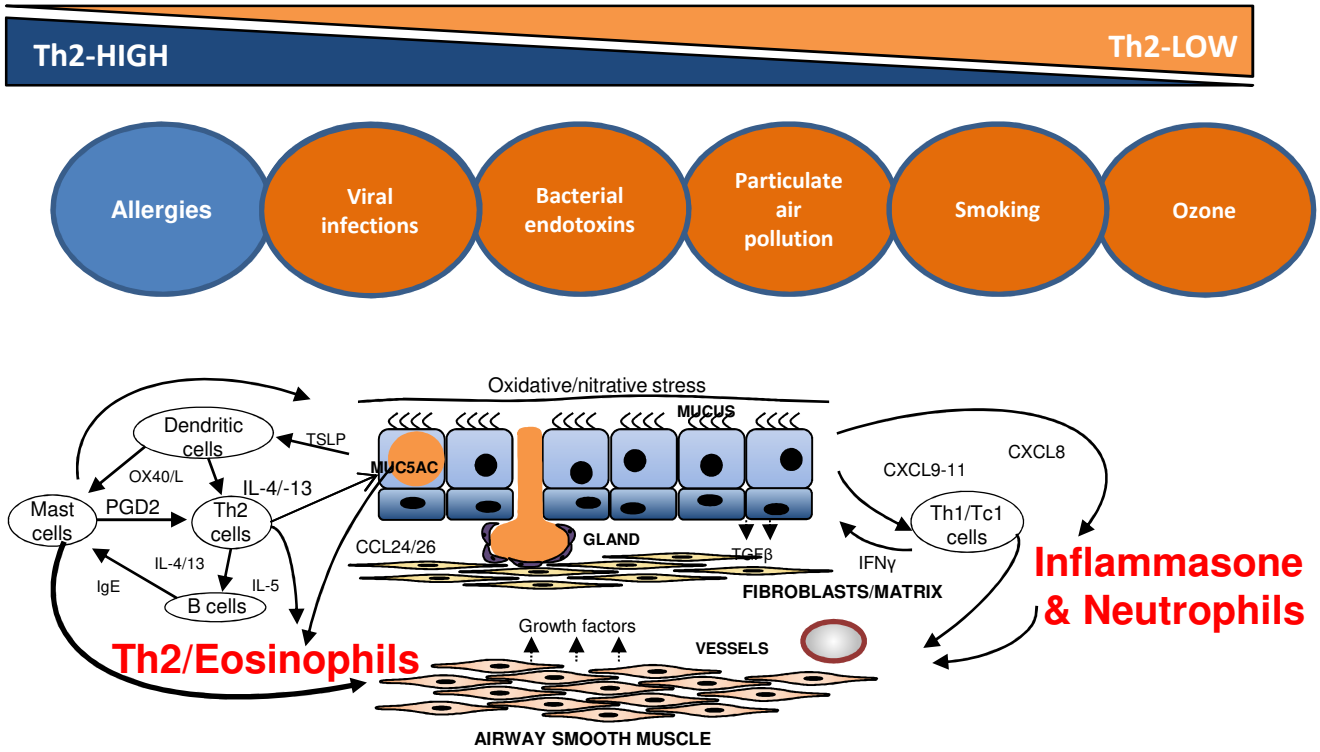
Sputum proteomics based asthma clusters (fingerprints)



www.ubiopred.eu

Burg et al (unpublished)

Pathobiology of Airway Disease



ANTI- IgE, IL-4/13, IL-5(R), GM-CSF, TGFβ, IL-17, IL-8, IL-6, IL-18, IL-1β(R), TNFα

Therapeutic antibodies assessed in clinical development

- **Cytokines released by immune-inflammatory and airway structural cells contribute to asthma inflammation[1]**
- **Research has identified several potential cytokine targets for anti-asthma therapy[2–4]**

Therapeutic antibody	Target	Therapeutic antibody	Target
Infliximab	TNF-α	Mepolizumab	IL-5
Golimumab	TNF-α	Benralizumab	IL-5R
Etanercept	TNF-α	Reslizumab	IL-5
Daclizumab	IL-2R (CD25)	QAX576[4]	IL-13
Secukinumab	IL-17A	Tralokinumab	IL-13
Brodalumab	IL-17	Lebrikizumab	IL-13
		Dupilumab[4]	IL-4R/IL-13R

1. Lambrecht BN & Hammad H. *Nat Immunol* 2015; 16:45–56; 2. Gallelli L, *et al. Biomed Res Int* 2013; 2013:104315;
3. Menzella F, *et al. Multidiscip Respir Med* 2015;10:1; 4. https://clinicaltrials.gov/ct2/home.

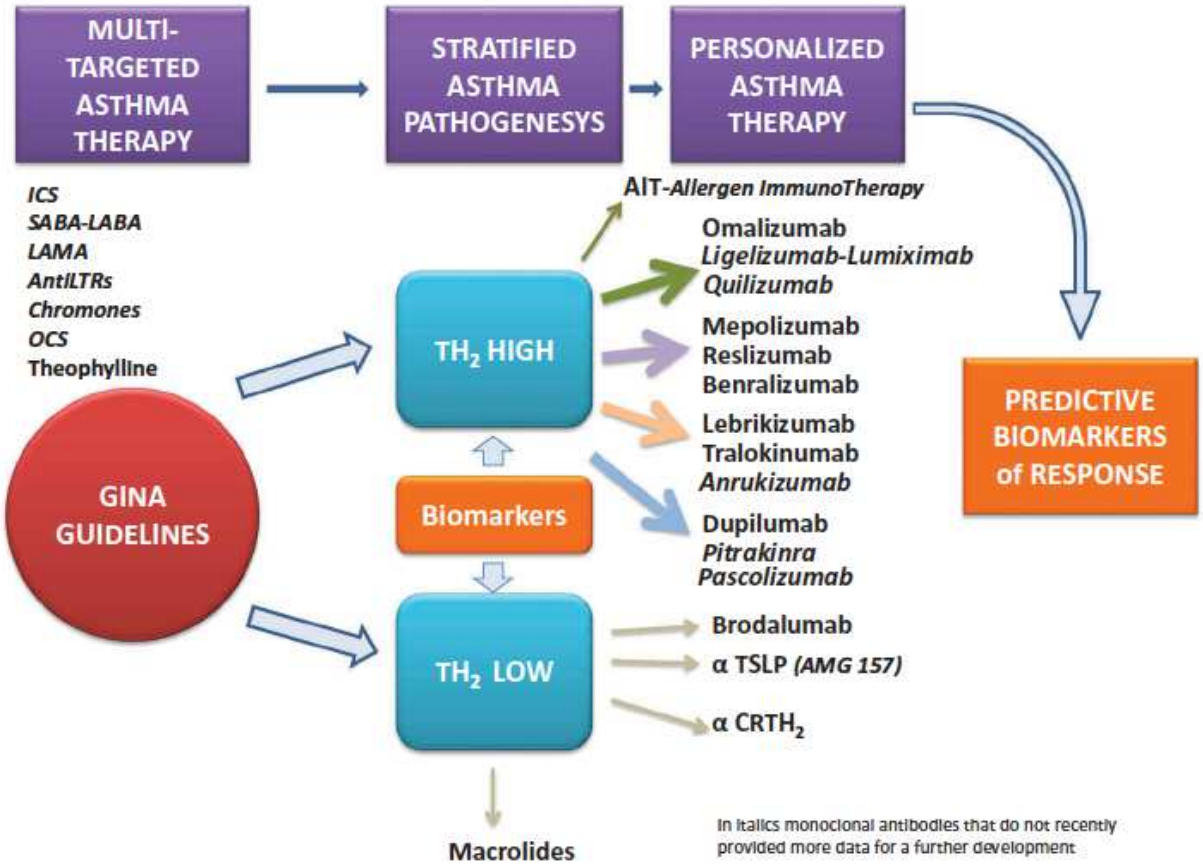
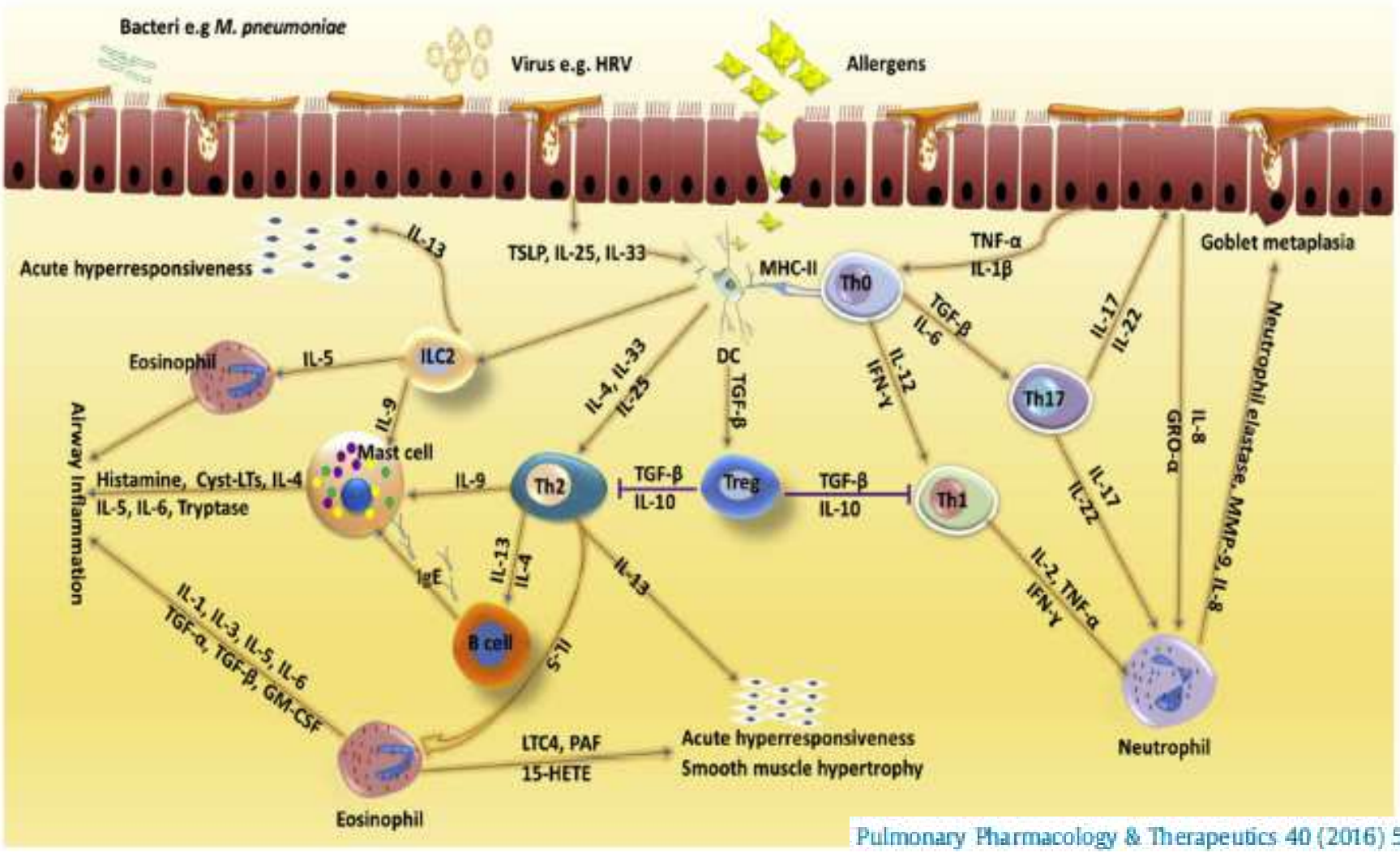


Figure 1. From mass target to personalized therapy through identification of different phenotypes/endotypes and development of biological tools directed to specific targets.

Bagnasco et al.,Exp.Rev.Resp.Med.2016

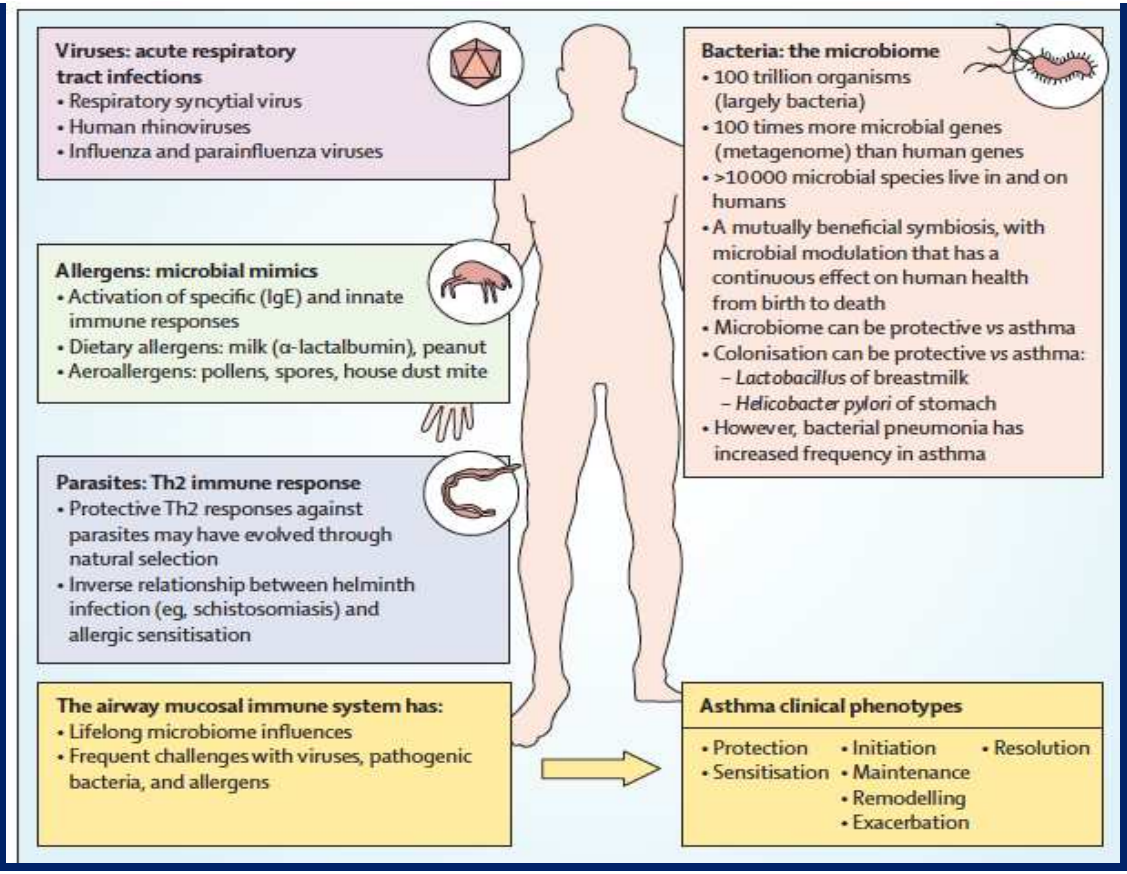


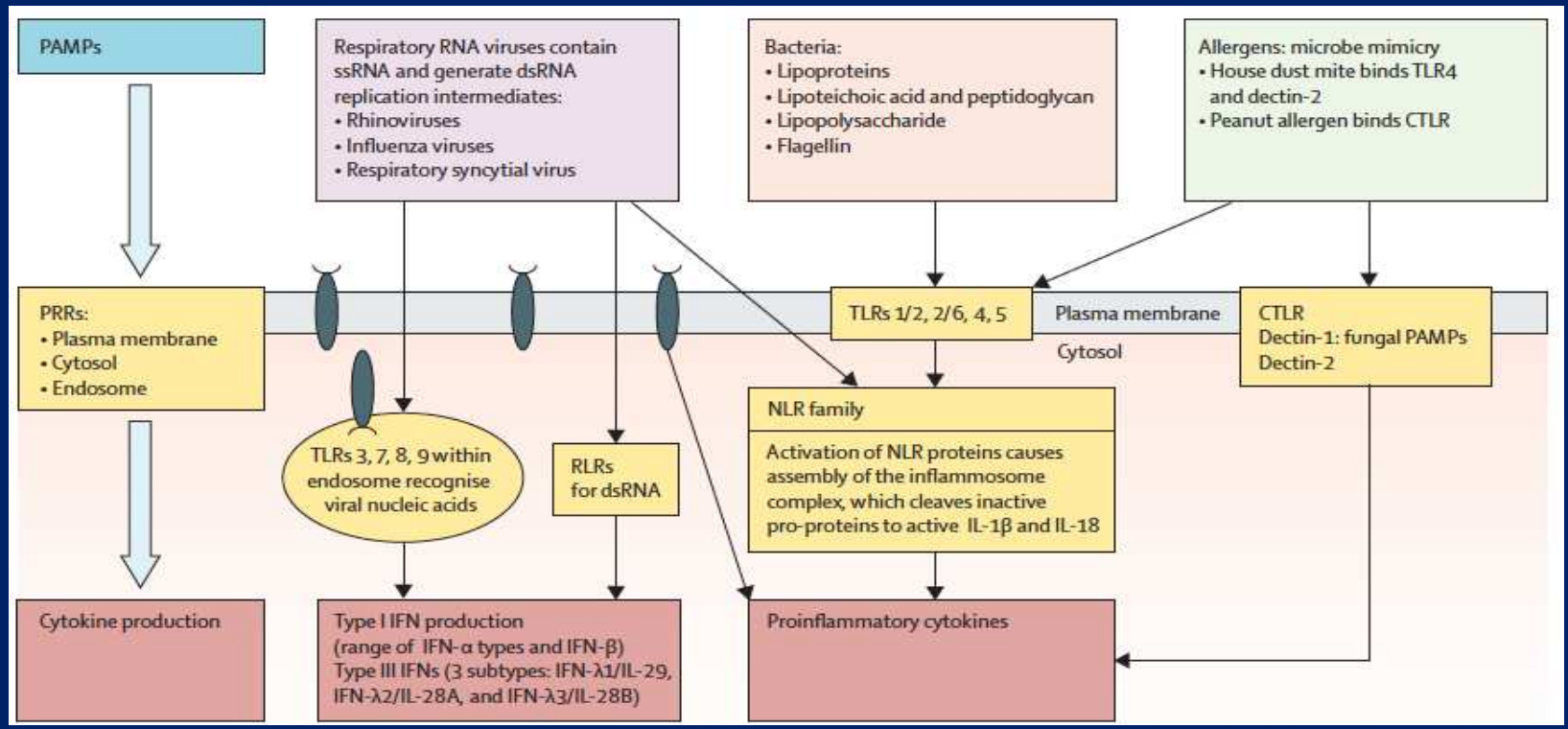
Pulmonary Pharmacology & Therapeutics 40 (2016) 52–68

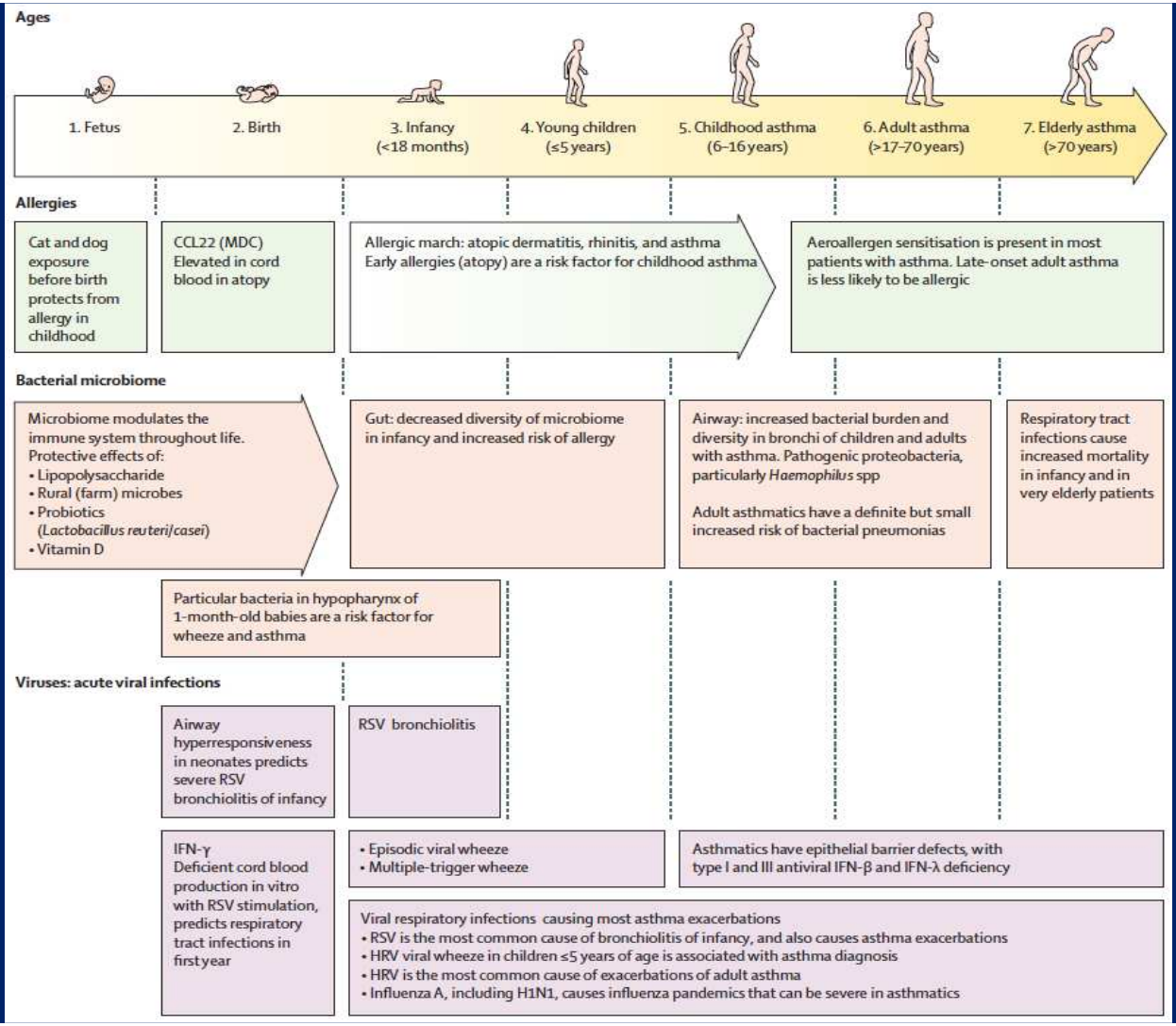
Microbes and mucosal immune responses in asthma

Trevor T Hansel, Sebastian L Johnston, Peter J Openshaw**

Lancet 2013; 381: 861–73




PAMPs
Respiratory RNA viruses contain ssRNA and generate dsRNA replication intermediates:
• Rhinoviruses
• Influenza viruses
• Respiratory syncytial virus
Bacteria:
• Lipoproteins
• Lipoteichoic acid and peptidoglycan
• Lipopolysaccharide
• Flagellin
Allergens: microbe mimicry
• House dust mite binds TLR4 and dectin-2
• Peanut allergen binds CTLR
PRRs:
• Plasma membrane
• Cytosol
• Endosome
TLRs 1/2, 2/6, 4, 5
Plasma membrane
Cytosol
CTLR
Dectin-1: fungal PAMPs
Dectin-2
NLR family
Activation of NLR proteins causes assembly of the inflammosome complex, which cleaves inactive pro-proteins to active IL-1β and IL-18
TLRs 3, 7, 8, 9 within endosome recognise viral nucleic acids
RLRs for dsRNA
Cytokine production
Type I IFN production
(range of IFN-α types and IFN-β)
Type III IFNs (3 subtypes: IFN-λ1/IL-29, IFN-λ2/IL-28A, and IFN-λ3/IL-28B)
Proinflammatory cytokines


Ages
1. Fetus
2. Birth
3. Infancy (<18 months)
4. Young children (≤5 years)
5. Childhood asthma (6–16 years)
6. Adult asthma (>17–70 years)
7. Elderly asthma (>70 years)
Allergies
Cat and dog exposure before birth protects from allergy in childhood
CCL22 (MDC) Elevated in cord blood in atopy
Allergic march: atopic dermatitis, rhinitis, and asthma
Early allergies (atopy) are a risk factor for childhood asthma
Aeroallergen sensitisation is present in most patients with asthma. Late-onset adult asthma is less likely to be allergic
Bacterial microbiome
Microbiome modulates the immune system throughout life.
Protective effects of:
• Lipopolysaccharide
• Rural (farm) microbes
• Probiotics (Lactobacillus reuteri/casei)
• Vitamin D
Gut: decreased diversity of microbiome in infancy and increased risk of allergy
Airway: increased bacterial burden and diversity in bronchi of children and adults with asthma. Pathogenic proteobacteria, particularly Haemophilus spp
Adult asthmatics have a definite but small increased risk of bacterial pneumonias
Respiratory tract infections cause increased mortality in infancy and in very elderly patients
Particular bacteria in hypopharynx of 1-month-old babies are a risk factor for wheeze and asthma
Viruses: acute viral infections
Airway hyperresponsiveness in neonates predicts severe RSV bronchiolitis of infancy
RSV bronchiolitis
IFN-γ Deficient cord blood production in vitro with RSV stimulation, predicts respiratory tract infections in first year
• Episodic viral wheeze
• Multiple-trigger wheeze
Asthmatics have epithelial barrier defects, with type I and III antiviral IFN-β and IFN-λ deficiency
Viral respiratory infections causing most asthma exacerbations
• RSV is the most common cause of bronchiolitis of infancy, and also causes asthma exacerbations
• HRV viral wheeze in children ≤5 years of age is associated with asthma diagnosis
• HRV is the most common cause of exacerbations of adult asthma
• Influenza A, including H1N1, causes influenza pandemics that can be severe in asthmatics

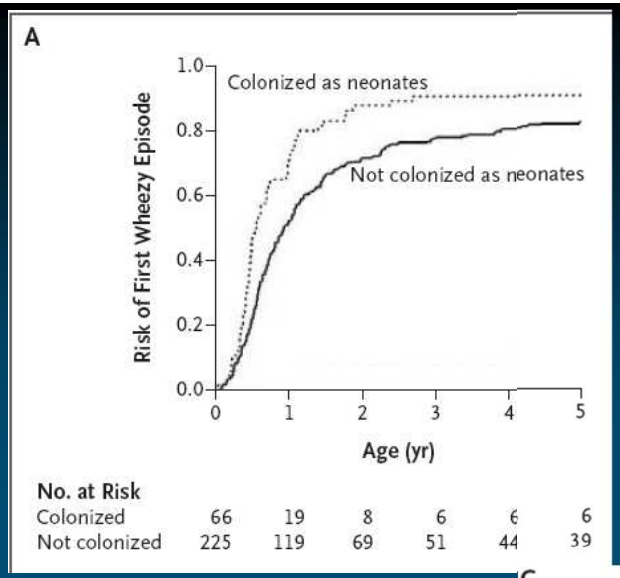
- **Throughout life, the human immune system interacts dynamically with microbes, allergens, dietary constituents, and metabolites**
- **The main goal is to develop molecular biomarkers to stratify disease pathways and personalise therapy for the individual patient, leading to optimum treatment of those patients with difficult-to-treat asthma**

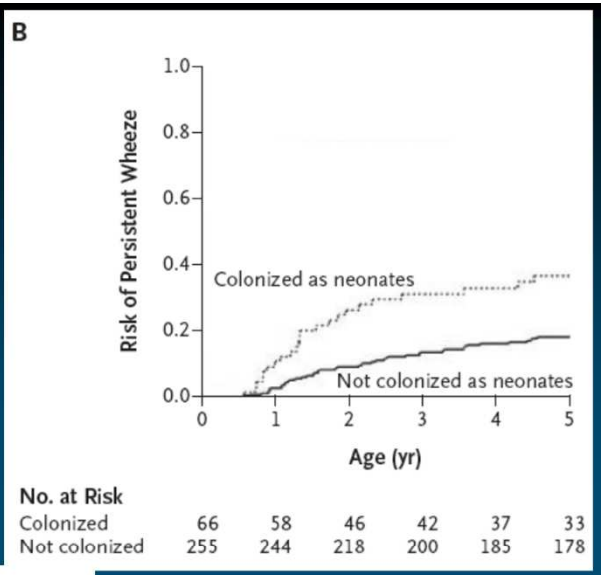
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2007;357:1487-95.

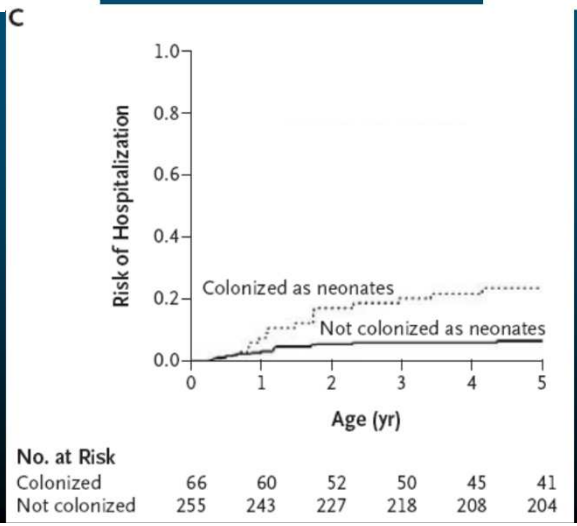
ORIGINAL ARTICLE

Childhood Asthma after Bacterial Colonization of the Airway in Neonates

Hans Bisgaard, M.D., D.M.Sc., Mette Northman Hermansen, M.D., Frederik Buchvald, M.D., Ph.D., Lotte Loland, M.D., Ph.D., Liselotte Brydensholt Halkjaer, M.D., Ph.D., Klaus Bønnelykke, M.D., Martin Brasholt, M.D., Andreas Heltberg, M.D., Nadja Hawwa Vissing, M.D., Sannie Vester Thorsen, M.Sc., Malene Stage, M.Sc., and Christian Bressen Pipper, M.Sc., Ph.D.


A
Risk of First Wheezy Episode
1.0
0.8
0.6
0.4
0.2
0.0
Colonized as neonates
Not colonized as neonates
0
1
2
3
4
5
Age (yr)
No. at Risk
Colonized 66 19 8 6 6 6
Not colonized 225 119 69 51 44 39

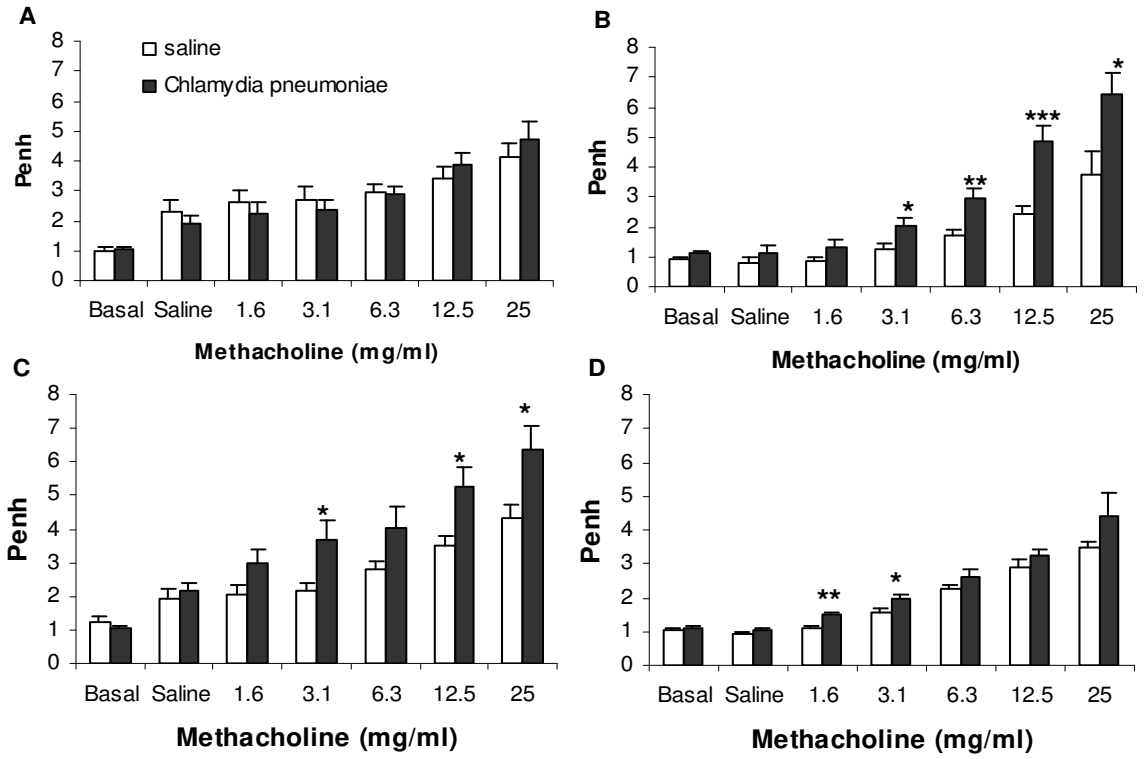

B
Risk of Persistent Wheeze
1.0
0.8
0.6
0.4
0.2
0.0
Colonized as neonates
Not colonized as neonates
0
1
2
3
4
5
Age (yr)
No. at Risk
Colonized 66 58 46 42 37 33
Not colonized 255 244 218 200 185 178


C
Risk of Hospitalization
1.0
0.8
0.6
0.4
0.2
0.0
Colonized as neonates
Not colonized as neonates
0
1
2
3
4
5
Age (yr)
No. at Risk
Colonized 66 60 52 50 45 41
Not colonized 255 243 227 218 208 204

Chlamydophila pneumoniae induces a sustained airway hyperresponsiveness and inflammation in mice

Francesco Blasi*[1], Stefano Aliberti[1], Luigi Allegra[1], Gioia Piatti[1], Paolo Tarsia[1], Jacobus M Ossewaarde[2], Vivienne Verweij[3], Frans P Nijkamp[3] and Gert Folkerts[3]

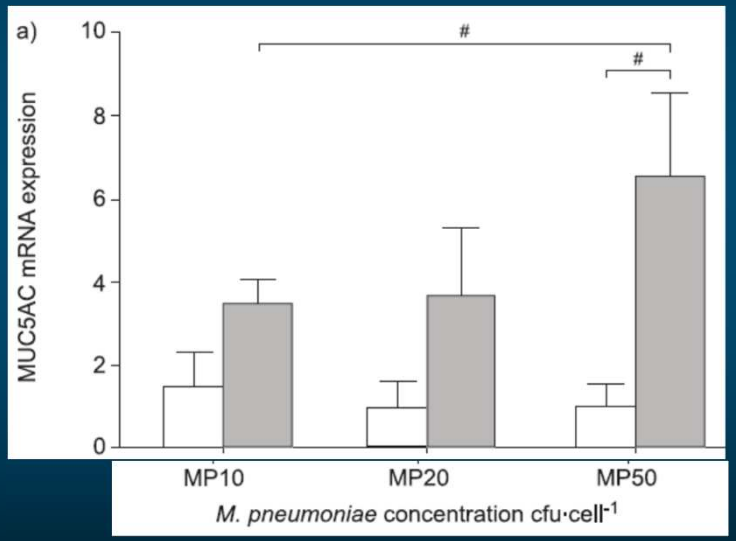
Respiratory Research 2007, **8**:83

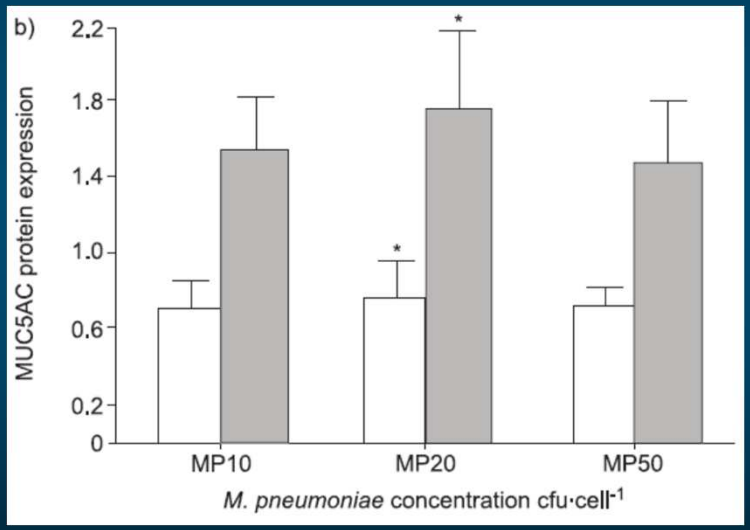


Eur Respir J 2008; 31: 43–46
DOI: 10.1183/09031936.00103307

Mycoplasma pneumoniae induces airway epithelial cell expression of MUC5AC in asthma

M. Kraft*, K.B. Adler#, J.L. Ingram*, A.L. Crews#, T.P. Atkinson¶, C.B. Cairns*, D.C. Krause+ and H.W. Chu§





Mycoplasma pneumoniae **exposure significantly increased MUC5AC mRNA and protein expression preferentially in airway epithelial cells isolated from asthmatic subjects. The toll-like receptor 2 pathway may be involved in this process.**

Mycoplasma pneumoniae and Asthma in Children

Sandra Biscardi,[1] Mathie Lorrot,[1] Elizabeth Marc,[1] Florence Moulin,[1] Benedicte Boutonnat-Faucher,[1] Claire Heilbronner,[1] Jean-Luc Iniguez,[1] Michèle Chaussain,[1] Elizabeth Nicand,[2] Josette Raymond,[1] and Dominique Gendrel[1]

The aim of this prospective study of a population of children (age, 2–15 years) hospitalized for severe asthma was to test them for acute infection due to *Mycoplasma pneumoniae* and acute infection due to *Chlamydia pneumoniae*. Of 119 patients with previously diagnosed asthma, acute *M. pneumionae* infection was found in 24 (20%) and *C. pneumoniae* infection was found in 4 (3.4%) of the patients during the current exacerbation. Of 51 patients experiencing their first asthma attack, acute *M. pneumoniae* infection was proven in 26 (50%) of the patients ($P < .01$) and *C. pneumoniae* in 4 (8.3%). In the control group of 152 children with stable asthma or rhinitis, 8 (5.2%) had *M. pneumoniae* infection ($P < .005$). Of the 29 patients experiencing their first asthma attack and infected with *M. pneumoniae* or *C. pneumoniae*, 18 (62%) had asthma recurrences but only 6 (27%) of the 22 patients who did not have such infections had asthma recurrences ($P < .05$). *M. pneumoniae* may play a role in the onset of asthma in predisposed children and could be a trigger for recurrent wheezing.

***Clin Infect Dis* 2004;38:1341-6**

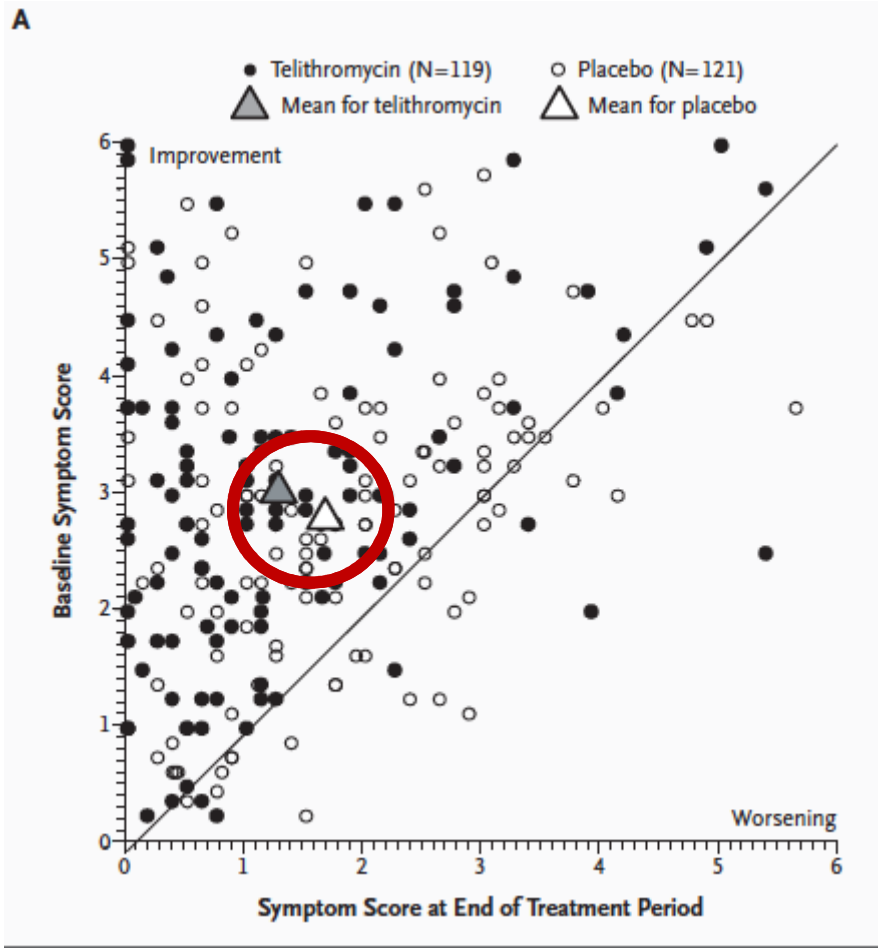
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Effect of Telithromycin in Acute Exacerbations of Asthma

Sebastian L. Johnston, M.D., Ph.D., Francesco Blasi, M.D., Peter N. Black, M.B., Ch.B., Richard J. Martin, M.D., David J. Farrell, Ph.D., and Richard B. Nieman, M.D., for the TELICAST Investigators*

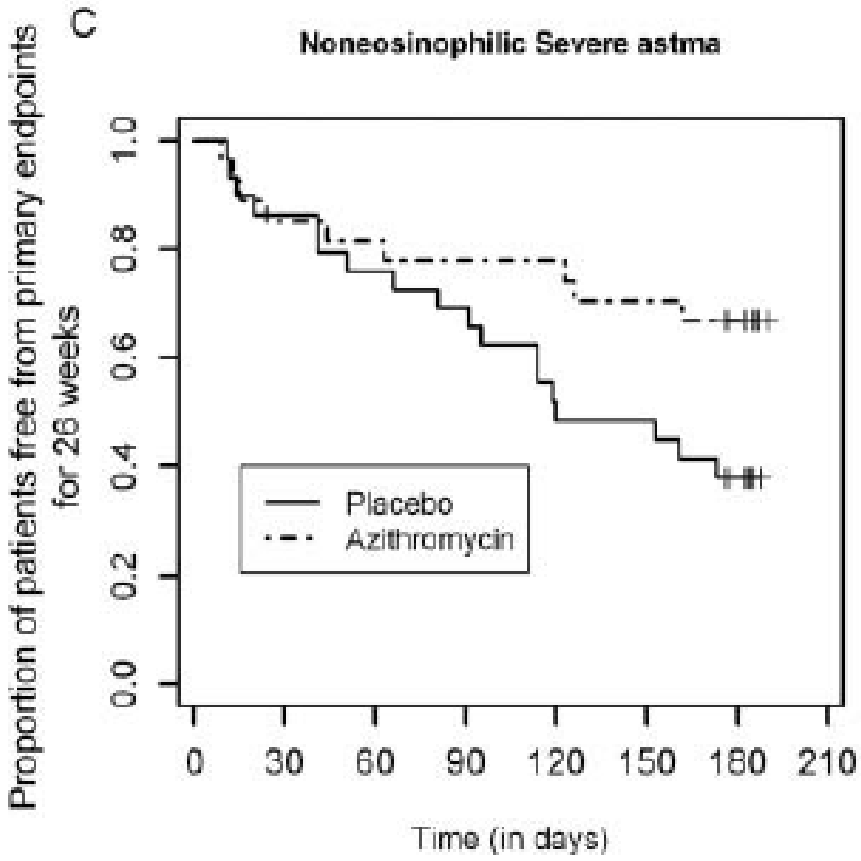
N Engl J Med 2006;354:1589-600.


A
Telithromycin (N=119)
Placebo (N=121)
Mean for telithromycin
Mean for placebo
Improvement
Worsening
Baseline Symptom Score
Symptom Score at End of Treatment Period
0
1
2
3
4
5
6

ORIGINAL ARTICLE

Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial

Guy G Brusselle,[1] Christine VanderStichele,[1] Paul Jordens,[2] René Deman,[3] Hans Slabbynck,[4] Veerle Ringoet,[5] Geert Verleden,[6] Ingel K Demedts,[7] Katia Verhamme,[8] Anja Delporte,[1] Bénédicte Demeyere,[1] Geert Claeys,[9] Jerina Boelens,[9] Elizaveta Padalko,[9] Johny Verschakelen,[10] Georges Van Maele,[11] Ellen Deschepper,[11] Guy F P Joos[1]


C
Noneosinophilic Severe astma
Proportion of patients free from primary endpoints for 26 weeks
0.0
0.2
0.4
0.6
0.8
1.0
0
30
60
90
120
150
180
210
Time (in days)
Placebo
Azithromycin

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

Jakob Stokholm, Bo L Chawes, Nadja H Vissing, Elín Bjarnadóttir, Tine M Pedersen, Rebecca K Vinding, Ann-Marie M Schoos, Helene M Wolsk, Sunna Thorsteinsdóttir, Henrik W Hallas, Lambang Arianto, Susanne Schjørring, Karen A Krogfelt, Thea K Fischer, Christian B Pipper, Klaus Bønnelykke, Hans Bisgaard

Implications of all the available evidence

Present guidelines do not recommend antibiotics for treatment of episodes of asthma-like symptoms in young children, yet antibiotics remain among the most commonly prescribed drugs in these episodes. Our findings suggest that azithromycin might be beneficial after medical assessment of an acute asthma-like episode in young children with a known history of such symptoms and without clinical signs of pneumonia. How the effect of azithromycin is compared with narrow-spectrum antibiotics and whether long-term effects are associated with recurrent use of azithromycin need to be investigated.

Lancet Respir Med 2016; 4: 19–26

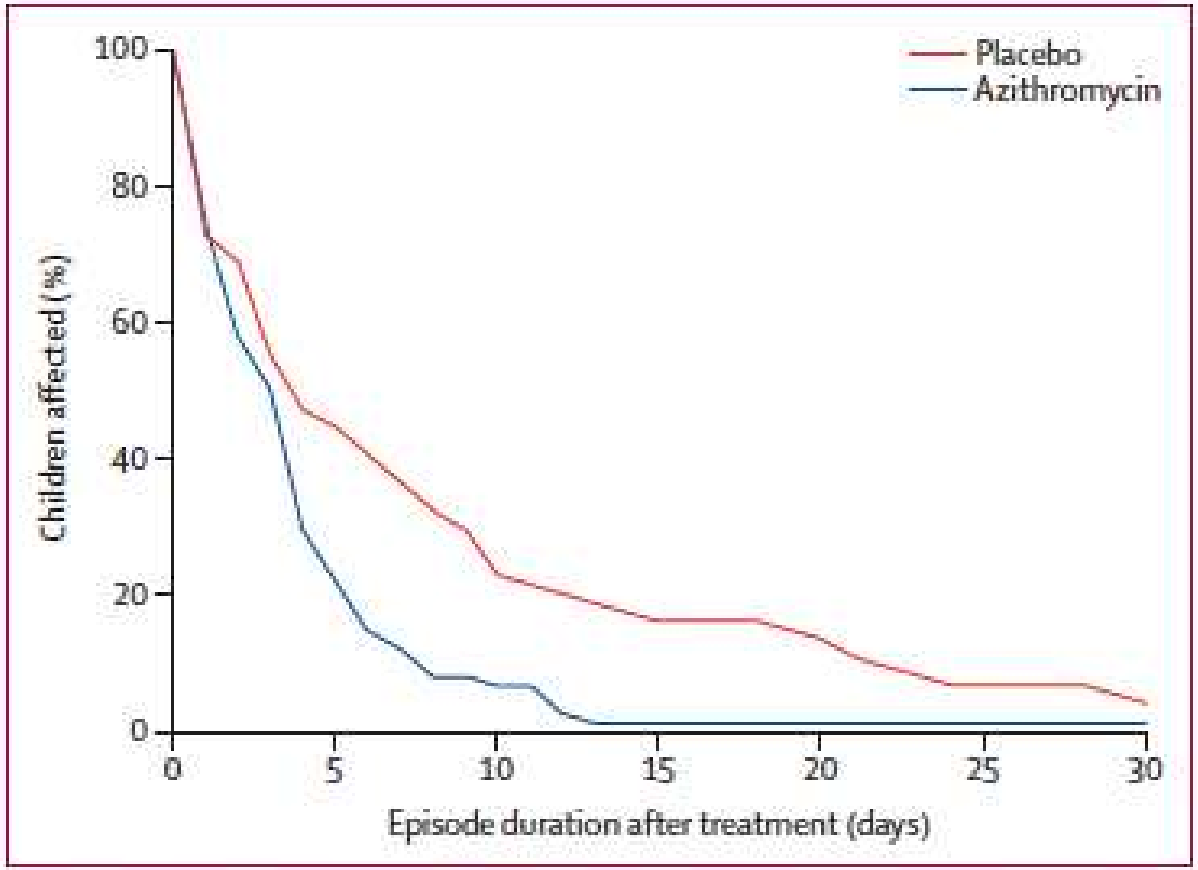


Figure 2: **Duration of episodes of troublesome lung symptoms after treatment**

Bacterial infection						
Any pathogenic bacteria	135 (100%)					0·2864
Present	90 (67%)	4·2	7·9	41·6% (–8·3 to 68·5)	0·0881	
Not present	45 (33%)	2·0	5·5	64·7% (35·6 to 80·7)	0·0007	
Haemophilus influenzae	135 (100%)					0·0323
Present	32 (24%)	2·7	12·1	77·0% (58·0 to 87·4)	<0·0001	
Not present	103 (76%)	3·8	5·9	33·4% (–28·7 to 65·6)	0·2264	
Moraxella catarrhalis	135 (100%)					0·9062
Present	64 (47%)	4·4	8·7	40·5% (–64·3 to 78·5)	0·3163	
Not present	71 (53%)	2·8	5·2	45·0% (1·7 to 69·3)	0·0436	
Streptococcus pneumoniae	135 (100%)					0·8576
Present	43 (32%)	3·3	6·2	44·4% (–22·1 to 74·7)	0·1436	
Not present	92 (68%)	3·6	7·5	49·6% (3·8 to 73·5)	0·0377	

Respiratory Medicine 119 (2016) 7–12

Contents lists available at ScienceDirect

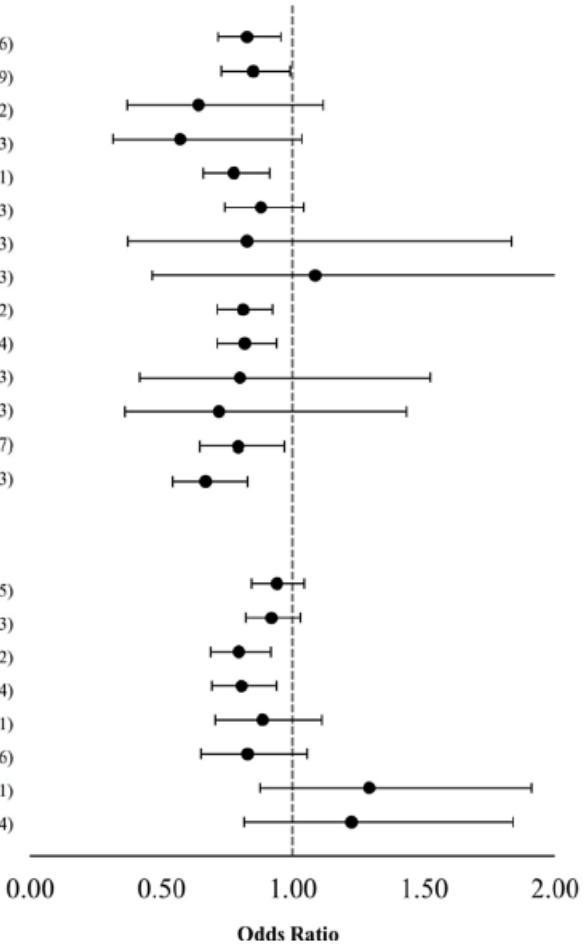
Respiratory Medicine

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

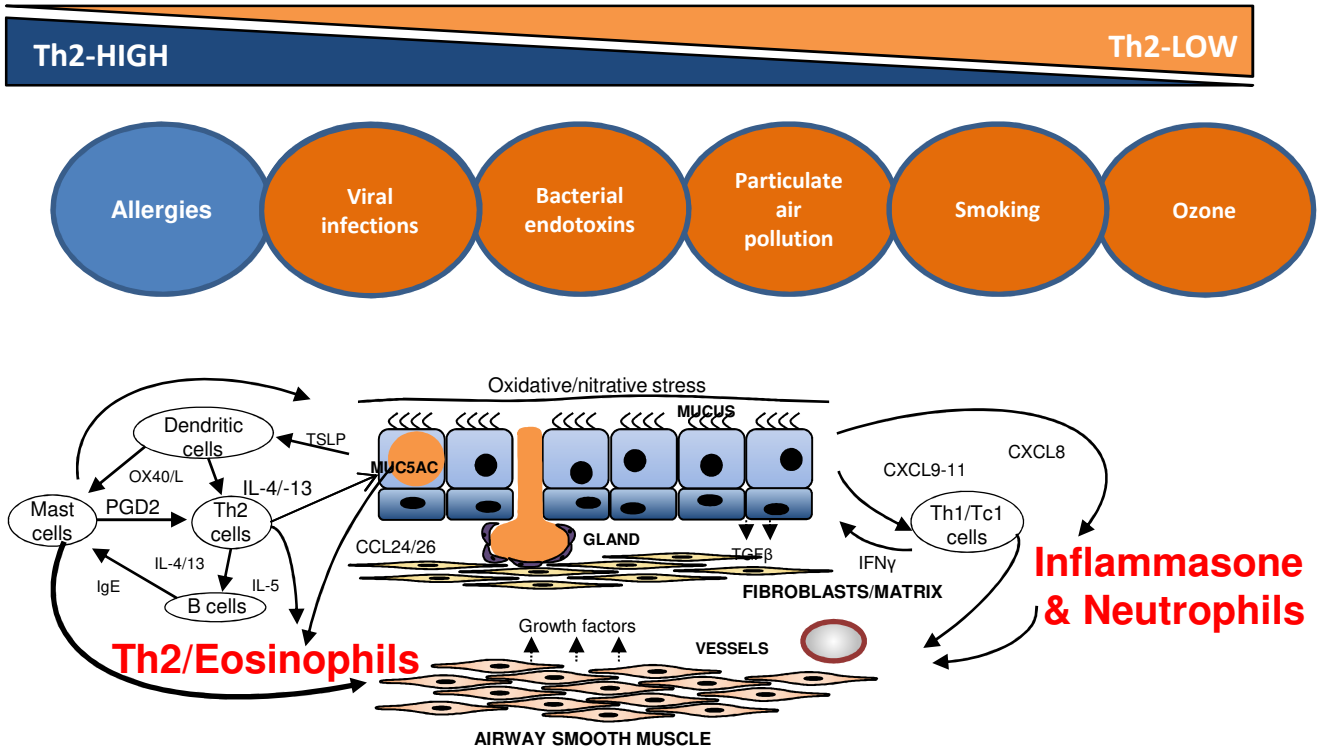
Respiratory drugs and macrolides prevent asthma exacerbations: A real-world investigation

Andrea Arfè [a], Francesco Blasi [b], Luca Merlino [c], Giovanni Corrao [a, *]

Drug exposure	Design	OR (95% CI)	Forest plot
Use of drugs for chronic respiratory diseases:			
ICS	CC	0.83 (0.72, 0.96)	
	CCTC	0.85 (0.73, 0.99)	
LABAs	CC	0.64 (0.37, 1.12)	
	CCTC	0.57 (0.31, 1.03)	
LABA/ICS	CC	0.78 (0.66, 0.91)	
	CCTC	0.88 (0.31, 1.03)	
LAMAs	CC	0.83 (0.37, 1.83)	
	CCTC	1.09 (0.46, 2.53)	
SABAs	CC	0.81 (0.71, 0.92)	
	CCTC	0.82 (0.71, 0.94)	
SAMAs	CC	0.80 (0.42, 1.53)	
	CCTC	0.71 (0.36, 1.43)	
Other respiratory drugs	CC	0.79 (0.65, 0.97)	
	CCTC	0.66 (0.54, 0.83)	
Use of antibiotics:			
Beta-lactams	CC	0.94 (0.84, 1.05)	
	CCTC	0.91 (0.82, 1.03)	
Macrolides	CC	0.79 (0.69, 0.92)	
	CCTC	0.81 (0.69, 0.94)	
Fluoroquinolones	CC	0.89 (0.70, 1.11)	
	CCTC	0.83 (0.65, 1.06)	
Other antibiotics	CC	1.29 (0.88, 1.91)	
	CCTC	1.23 (0.82, 1.84)	



Pathobiology of Airway Disease



ANTI- IgE, IL-4/13, IL-5(R), GM-CSF, TGFβ, IL-17, IL-8, IL-6, IL-18, IL-1β(R), TNFα