Pediatria preventiva e sociale

Pidotimod: non solo IRR

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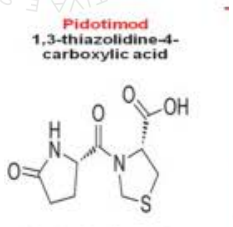
Napoli, 25 settembre 2022

DIPARTIMENTO DI SCIENZE MEDICHE TRASLAZIONALI
UNIVERSITÀ DEGLI STUDI DI NAPOLI - FEDERICO II

Pidotimod

3-L-pyroglutamyl-L-thiaziolidine-4carboxylic acid



A synthetic dipeptide molecule with immunomodulatory properties [*Int J Immunopathol Pharmacol. 2009*].

Highly purified molecule, rapidly absorbed by the GI tract, with a bioavailability of 45% eliminated unmodified via renal excretory mechanisms [*Arzneimittelforschung. 1994]*

Good safety profile

No serious adverse events reported in human studies

Pidotimod: properties

-Immunomodulatory activity on innate/adaptive immune response

-Induces dendritic cell (DC) maturation

-Upregulates the expression of HLA-DR and co-stimulatory molecules CD83 and CD86

-Stimulates DCs to release pro-inflammatory molecules, driving T cell towards Th1 phenotype

-Enhances natural killer cell functions

-Inhibits thymocyte apoptosis

-Promotes phagocytosis

Pharmacol Res. 1992; Immunopharmacol Immunotoxicol. 1992

Pidotimod: non solo IRR

Agenda

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2. Pidotimod & atopic rhinosinusitis
3. Pidotimod & wheezing/ asthma
4. Pidotimod & PFAFA
5. Conclusions

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Pidotimod & infectious disorders (not RRI)

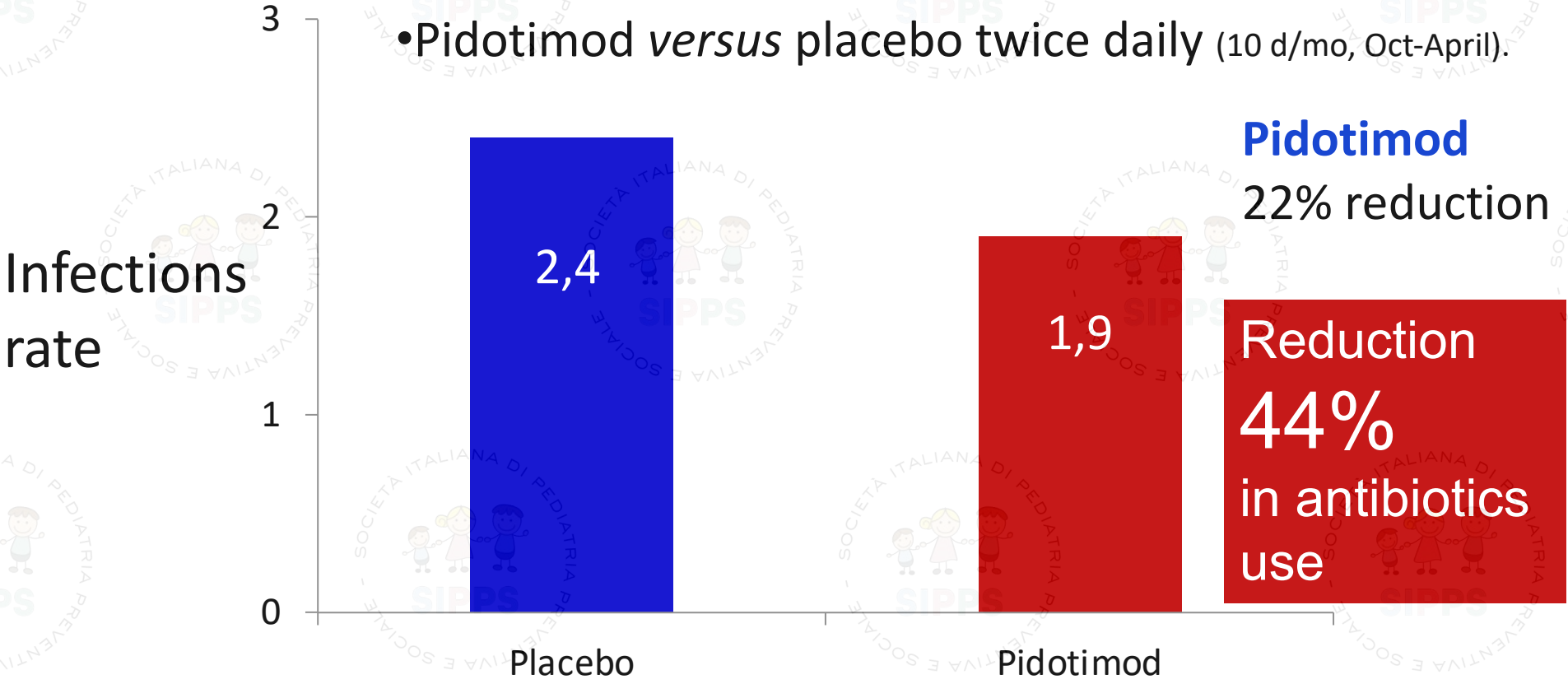
Airways – Acute Infections

Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study

Chiara Mameli[a], Angela Pasinato[b], Marina Picca[c], Giorgio Bedogni[d], Stefania Pisanelli[e], Gian Vincenzo Zuccotti[a,*], for the AX-Working group[1]

Pharmacological Research 97 (2015) 79–83

- **49 healthy 3-yr-old ch**. not yet attending day-care
- Pidotimod *versus* placebo twice daily (10 d/mo, Oct-April).



Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

2019

Effects of pidotimod and bifidobacteria mixture on clinical symptoms and urinary metabolomic profile of children with recurrent respiratory infections: a randomized placebo-controlled trial

Francesca Santamaria[a,*], Silvia Montella[a,**], Matteo Stocchero[b], Paola Pirillo[b,c], Sara Bozzetto[b], Giuseppe Giordano[b,c], Marco Poeta[a], Eugenio Baraldi[b,c]

Primary clinical endpoint

Symptom-free days

Days with common cold

Secondary metabolomic endpoint

Any change in the urine metabolomic profile.

before and after treatment with pidotimod 400 mg/d **and bifidobacteria mix**

Children with RRTIs aged 3–6 years attending nursery school/kindergarten

Pidotimod & infectious disorders (not RRI)

Airways

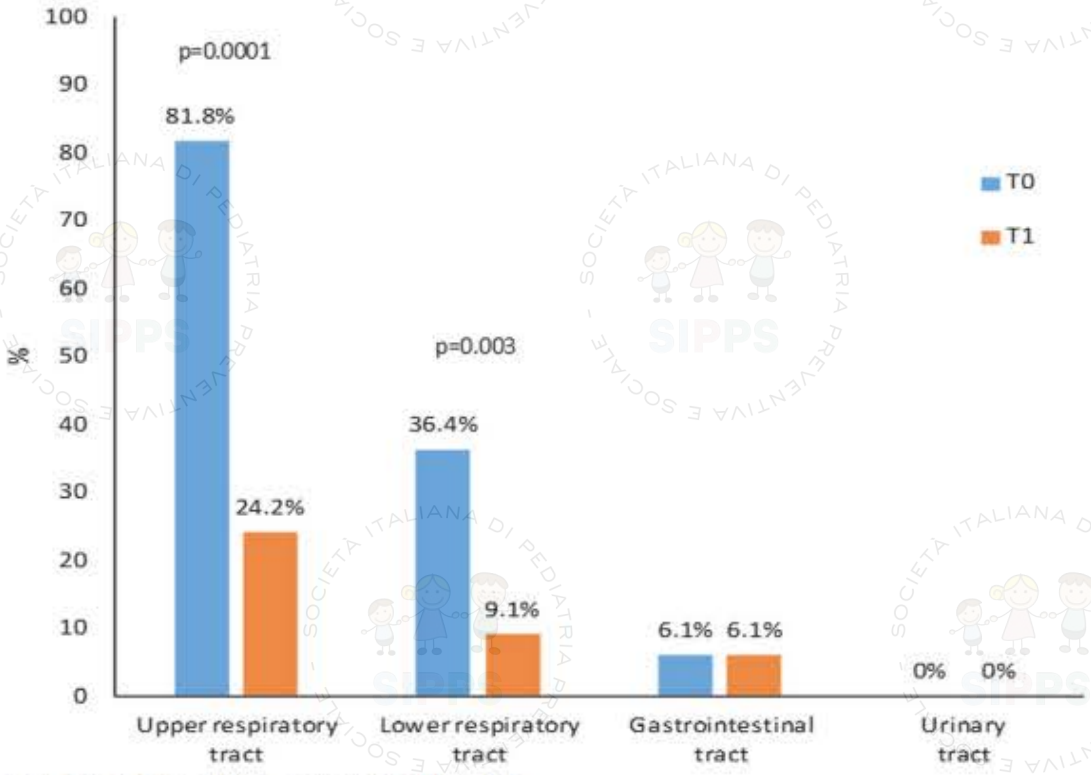
Effects of Pidotimod in children with Down syndrome (DS)
A retrospective Italian study. *Valentini, IJP 2020*

DS: high susceptibility to respiratory infections (immune defects; airways abnormalities)

Effect of PDT on immune & clinical parameters before (T0)/after (T1)

PDT 400 mg/d in the first 20 days of each month for 6 mo (Sept to Febr)

33 DS ch (age 6 yrs)



Pidotimod & infectious disorders (not RRI)

Airways

Comparison of T and B cells in the peripheral blood and B cell function in vitro at T0 and T1.

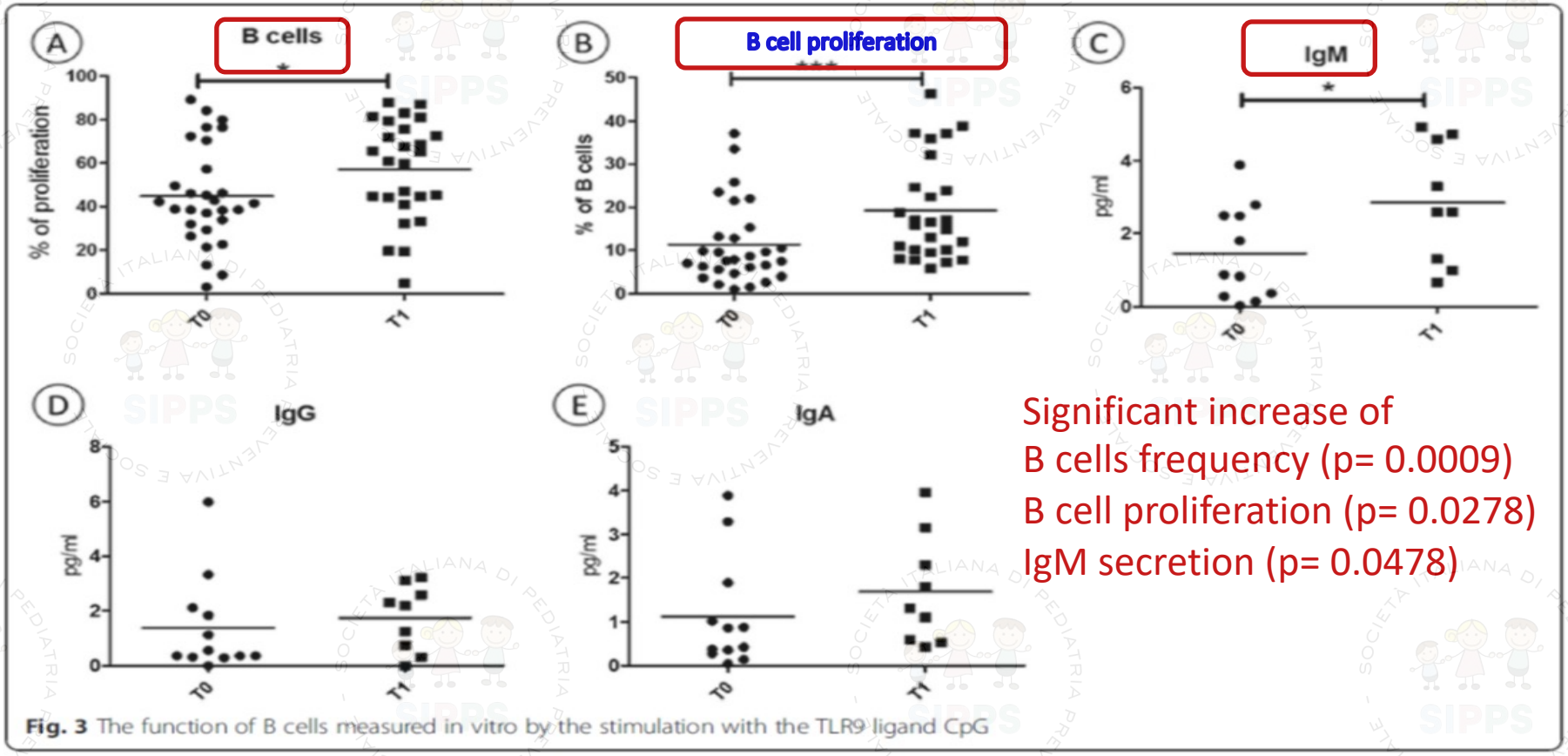


Fig. 3 The function of B cells measured in vitro by the stimulation with the TLR9 ligand CpG

Significant increase of
B cells frequency (p= 0.0009)
B cell proliferation (p= 0.0278)
IgM secretion (p= 0.0478)

Valentini, IJP 2020

Pidotimod & infectious disorders (not RRI)

Airways – Community Acquired Pneumonia

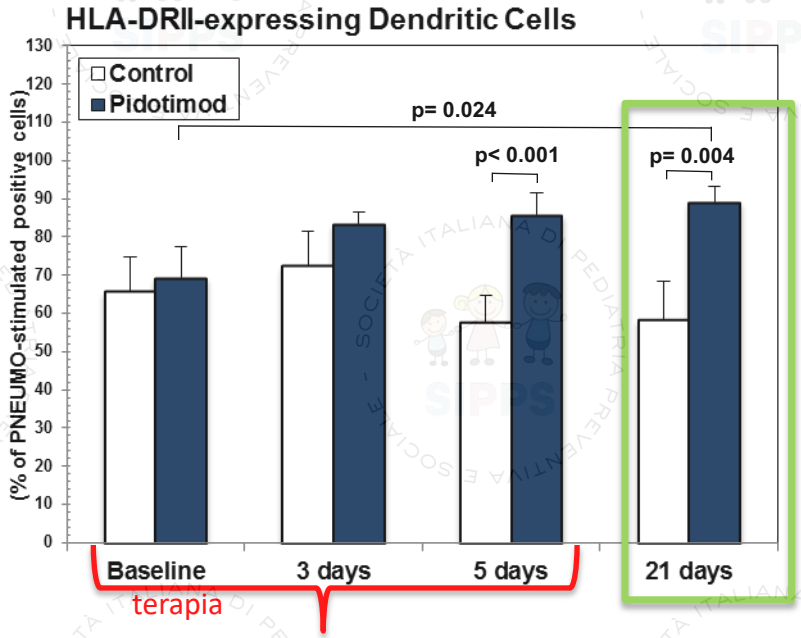
Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia. *Esposito, J Transl Med 2015*

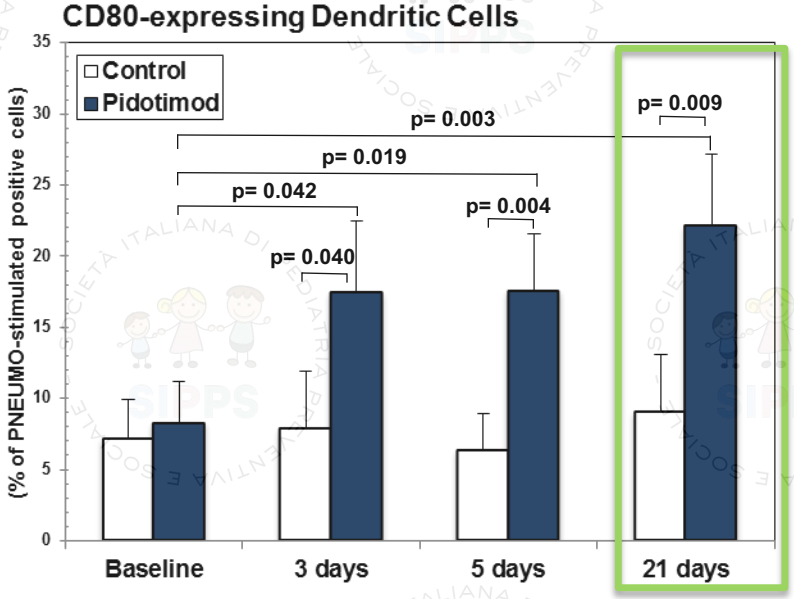
RCT of 20 children (> 3 yrs) with CAP (chest X ray +)

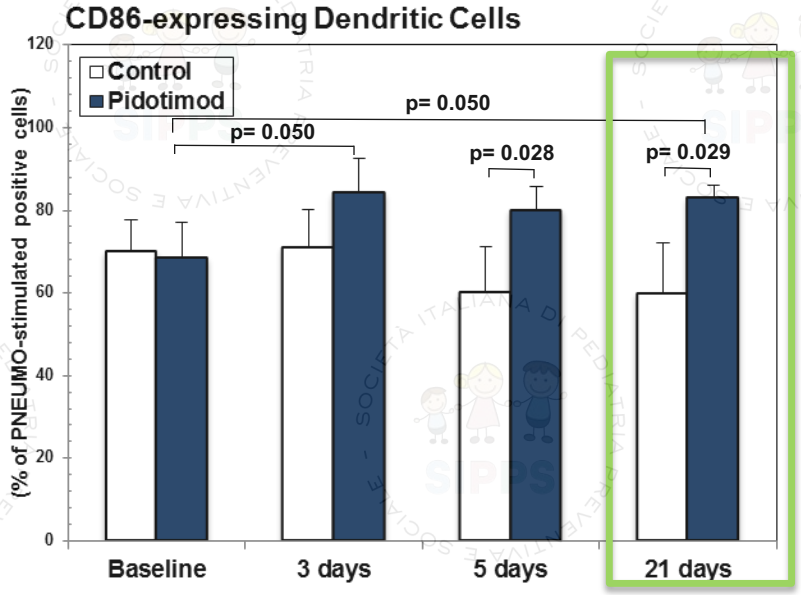
- Amoxi Clav 80 mg/kg/die per os + claritro 15 mg/kg/die per os (10-14 d) + PIDOTIMOD 400 mg x 2 volte/die (10 d)
- Amoxi Clav 80 mg/kg/die per os + claritro 15 mg/kg/die per os (10-14 d)
- Immunologic investigations T0 and at T3, T5 & T21 days

Pidotimod & infectious disorders (not RRI)

Airways – Community Acquired Pneumonia







Esposito, J Transl Med 2015

PIDOTIMOD up-regulates the levels of CD80 & CD86-expressing dendritic cells

Modified; courtesy of prof P Marchisio, 2022

Pidotimod & infectious disorders (not IRR)

Airways – Community Acquired Pneumonia

PDT administered together with standard antibiotics is associated with a favorable persistent immunomodulatory effect in children with CAP

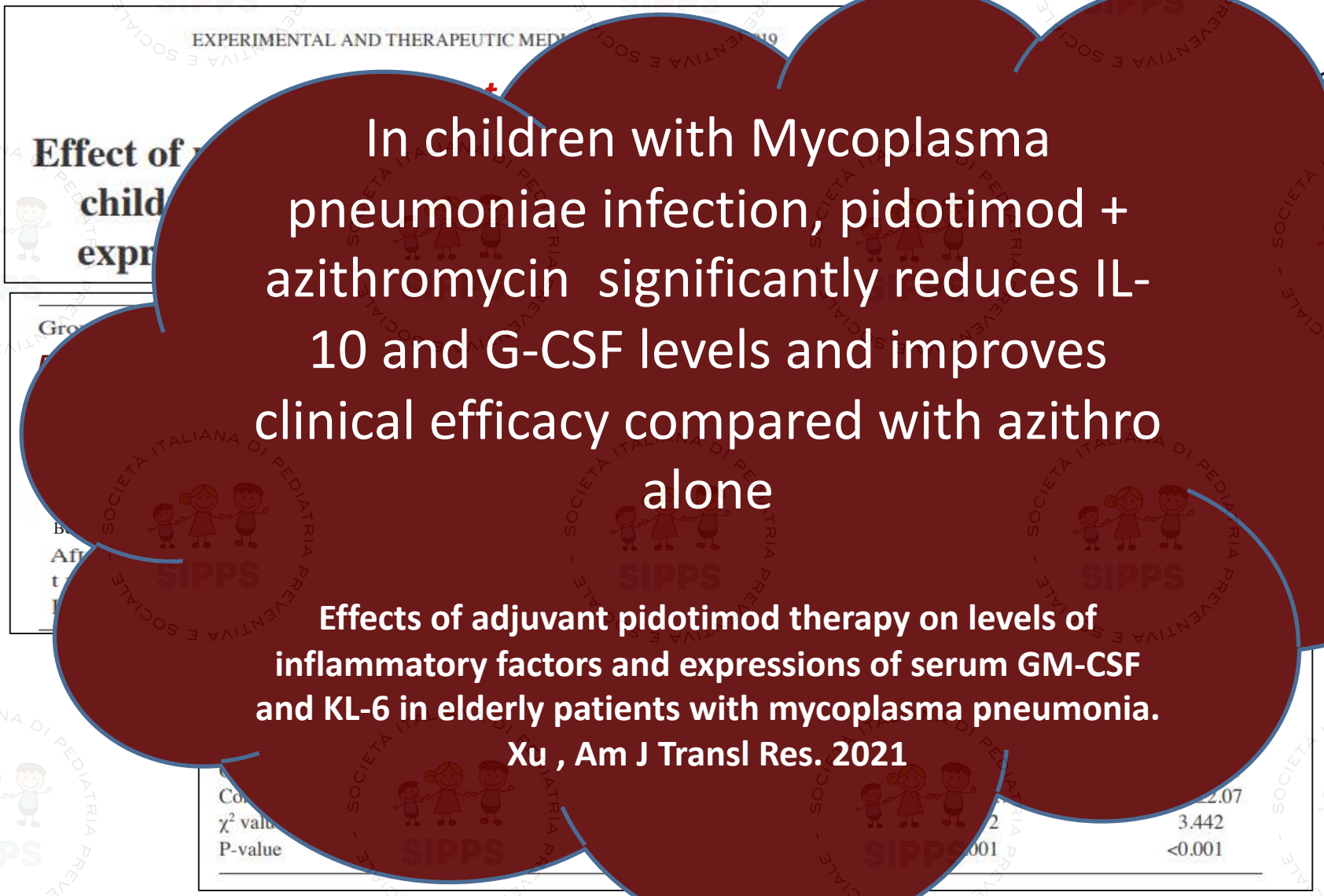
Esposito, J Transl Med 2015

Immunomodulatory effects of pidotimod in adults with CAP undergoing standard antibiotic therapy.

Trabattoni, Pulm Pharmacol Ther. 2017

Pidotimod & infectious disorders (not IRR)

Airways – Community Acquired Pneumonia



In children with Mycoplasma pneumoniae infection, pidotimod + azithromycin significantly reduces IL-10 and G-CSF levels and improves clinical efficacy compared with azithro alone

Effects of adjuvant pidotimod therapy on levels of inflammatory factors and expressions of serum GM-CSF and KL-6 in elderly patients with mycoplasma pneumonia.
Xu , Am J Transl Res. 2021

Total effective rate in observation group (95%) significantly higher vs control group (81%)

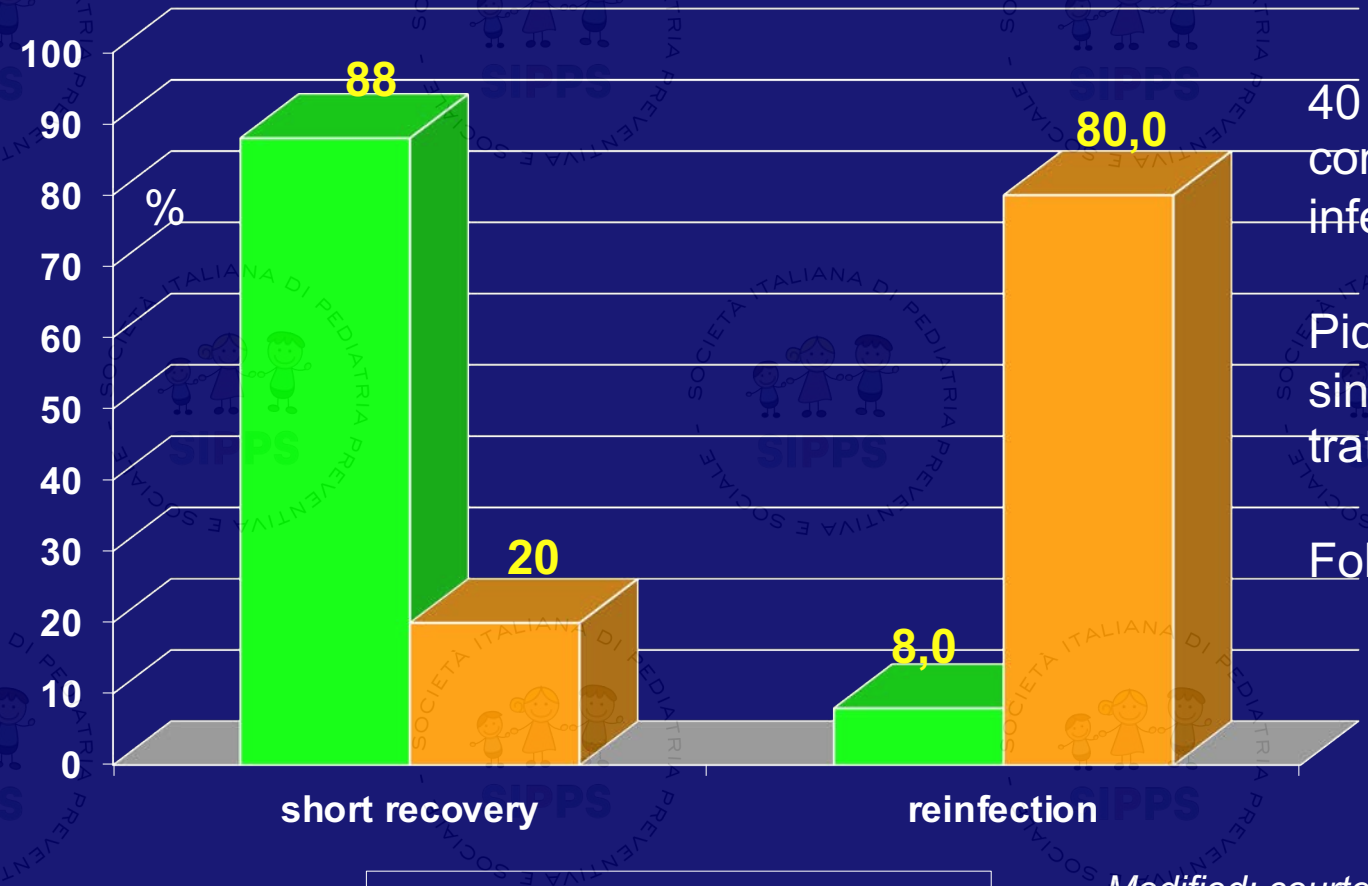
Pidotimod & infectious disorders (not RRI)

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 34, no. 4, 1597-1599 (2020)

LETTER TO THE EDITOR

Pidotimod in children with infectious mononucleosis: a preliminary randomized controlled study

I. La Mantia[1], A. Varricchio[2], C. Andaloro[1] and G. Ciprandi[3]



40 Bambini 7 – 16 anni con mononucleosi infettiva

Pidotimod da inizio sintomi x 30 gg vs trattamento standard.

Follow-up per 6 mesi

Modified; courtesy of prof P Marchisio, 2022

Pidotimod: non solo IRR

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Pidotimod & atopic rhinosinusitis

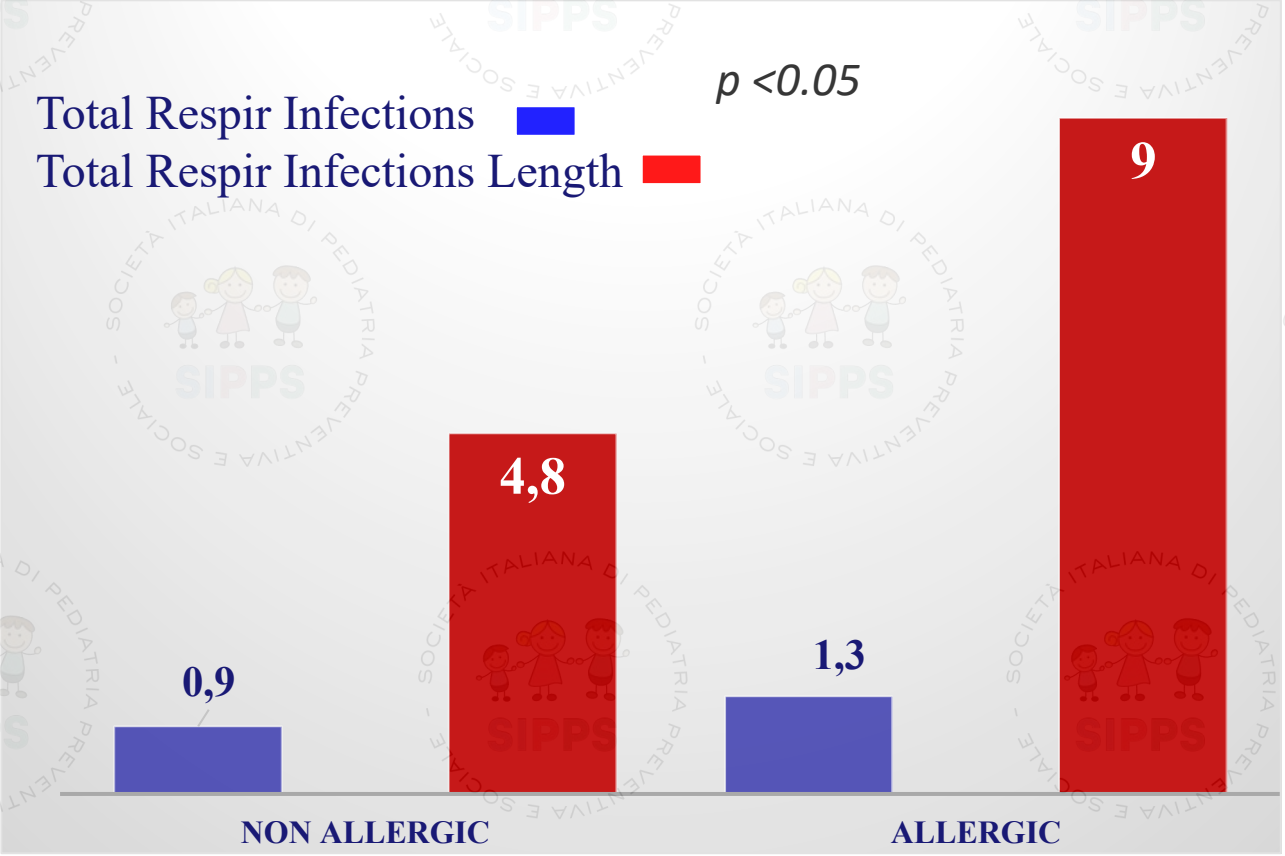
Allergic children have more numerous and severe respiratory infections than non-allergic children.

Ciprandi, Tosca, Fasce. Pediatr Allergy Immunol 2006

ATOPY

- Th2-polarization
- Physiological Th1-dependent mechanisms for fighting respiratory infections may be defective.

117 ch (4.02 yr) studied during the spring, 46 allergic



Pidotimod & atopic rhinosinusitis

Efficacy of Pidotimod use in treating allergic rhinitis in a pediatric population. *Brindisi, IJP 2020*

Although allergic rhinitis and adenoids hypertrophy have different etiopathogenesis, they share nasal mucosa chronic inflammation

↓

To evaluate the effect of PDT on nasal inflammation

26 children with allergic rhinitis (dust mites)
16 children with adenoid hypertrophy vs 13 healthy controls
15 children with both disorders

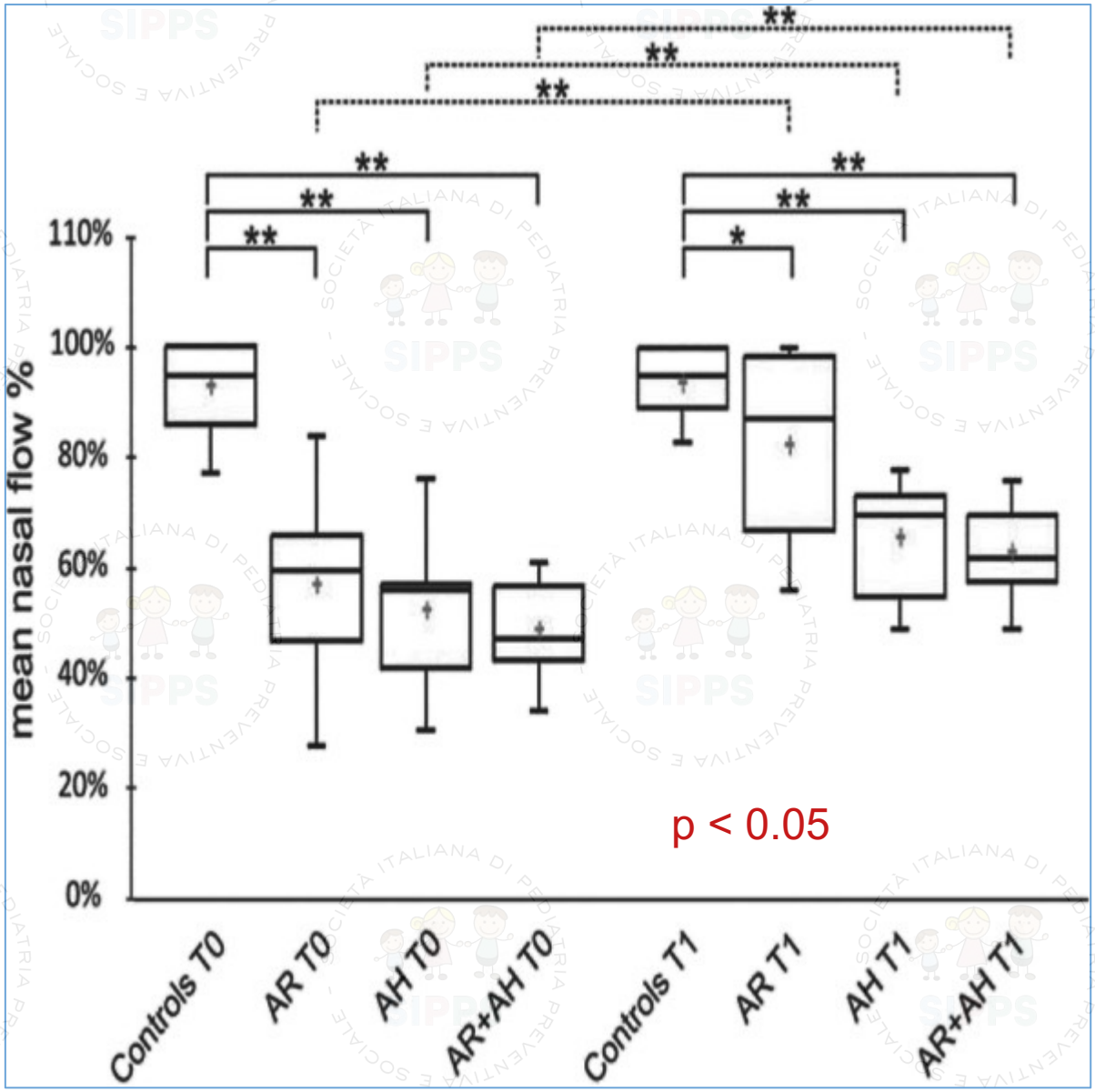
T0: skin prick tests, nasal fiberoptic endoscopy, anterior rhinomanometry, nasal swabs.

Pidotimod (1 vial 400/d for 30 days)
At T1 (after 1 month re-evaluation as at baseline).

Pidotimod & atopic rhinosinusitis

% nasal flow significantly different between groups before and after treatment with pidotimod

AR: allergic rhinitis
AH: adenoidal hypertrophy

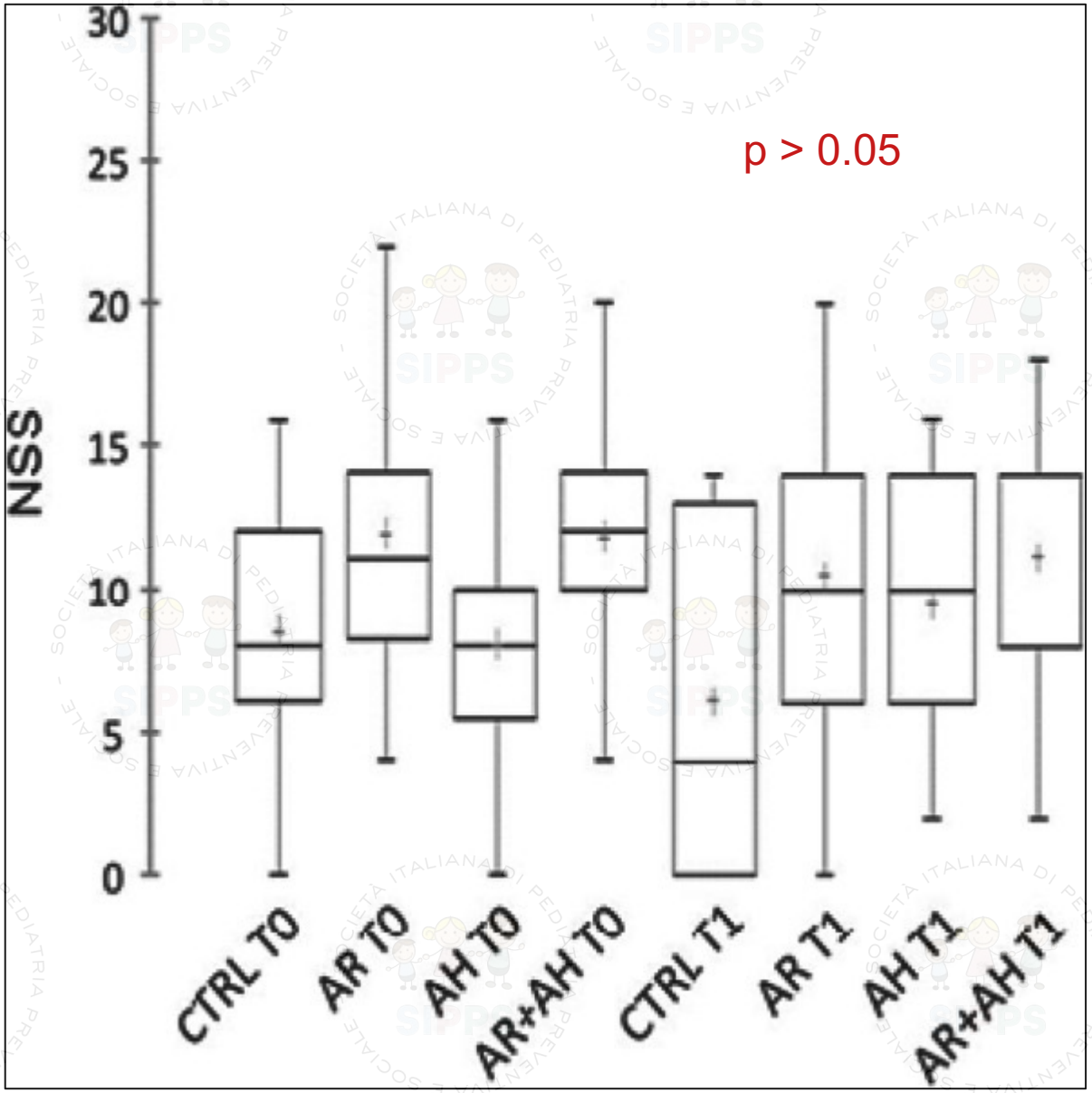


Brindisi, IJP 2020

Pidotimod & atopic rhinosinusitis

Nasal symptom score in AR and AH children and controls before and after treatment with pidotimod

AR: allergic rhinitis
AH: adenoidal hypertrophy



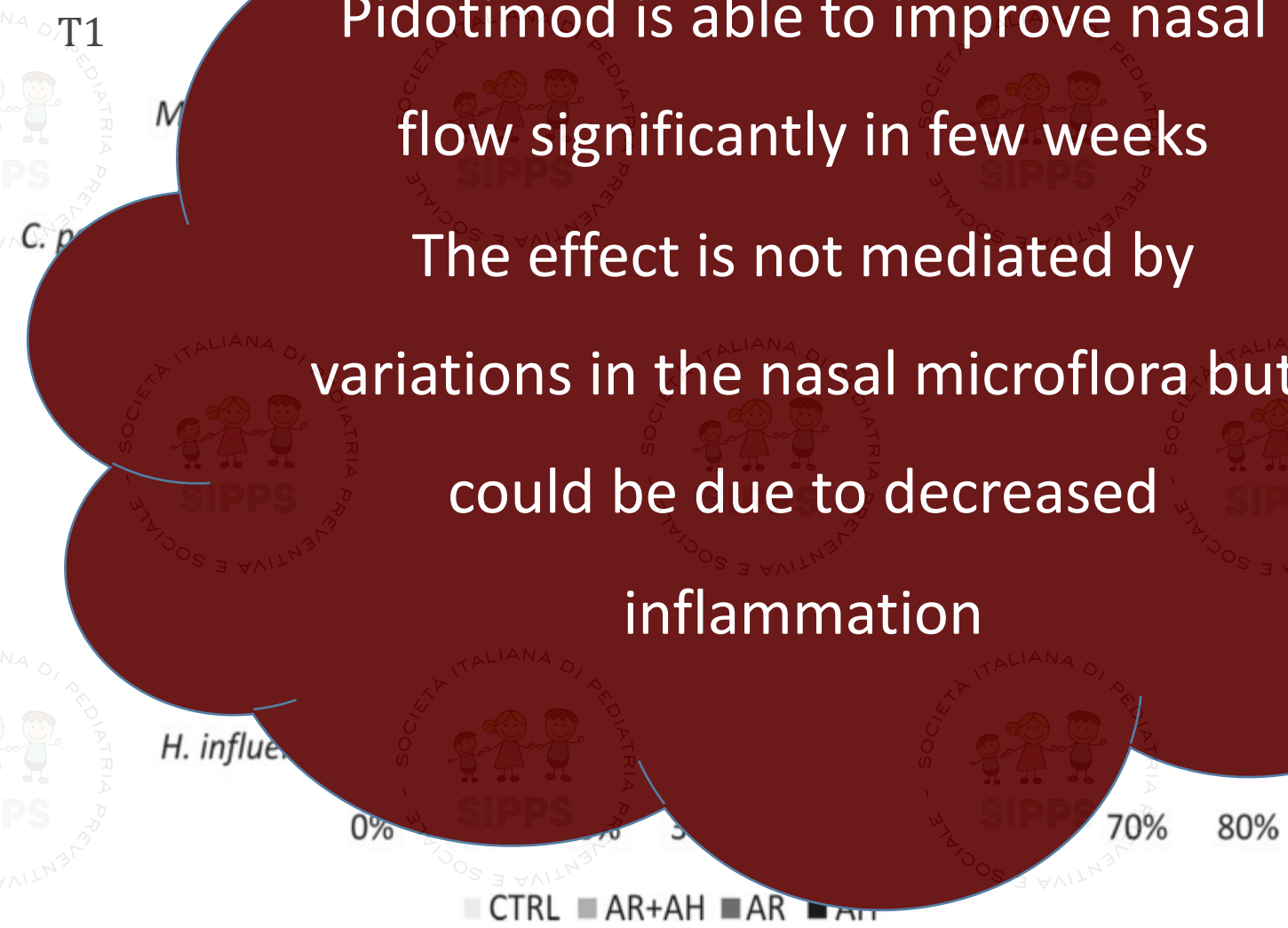
Brindisi, IJP 2020

Pidotimod & atopic rhinosinusitis

No effects on prevalence of bacterial species

Pidotimod is able to improve nasal flow significantly in few weeks

The effect is not mediated by variations in the nasal microflora but could be due to decreased inflammation



Brindisi, IJP 2020

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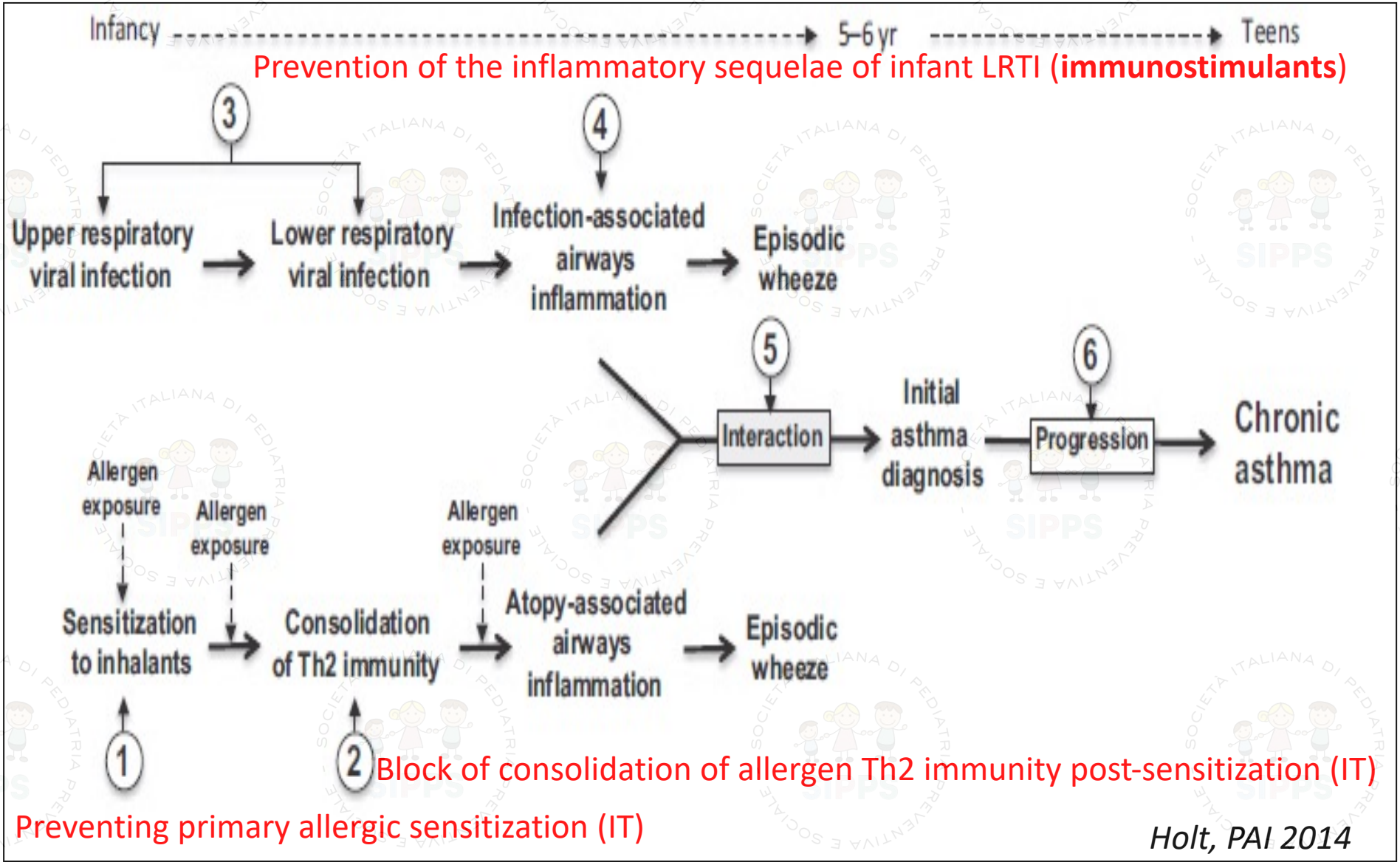
Pidotimod & wheezing and asthma

Causal pathways leading to asthma in childhood

A blueprint for development of preventive early intervention strategies.



Holt, PAI 2014

ANNALS OF THE AMERICAN THORACIC SOCIETY

A Journal for clinicians, clinical researchers, and medical educators

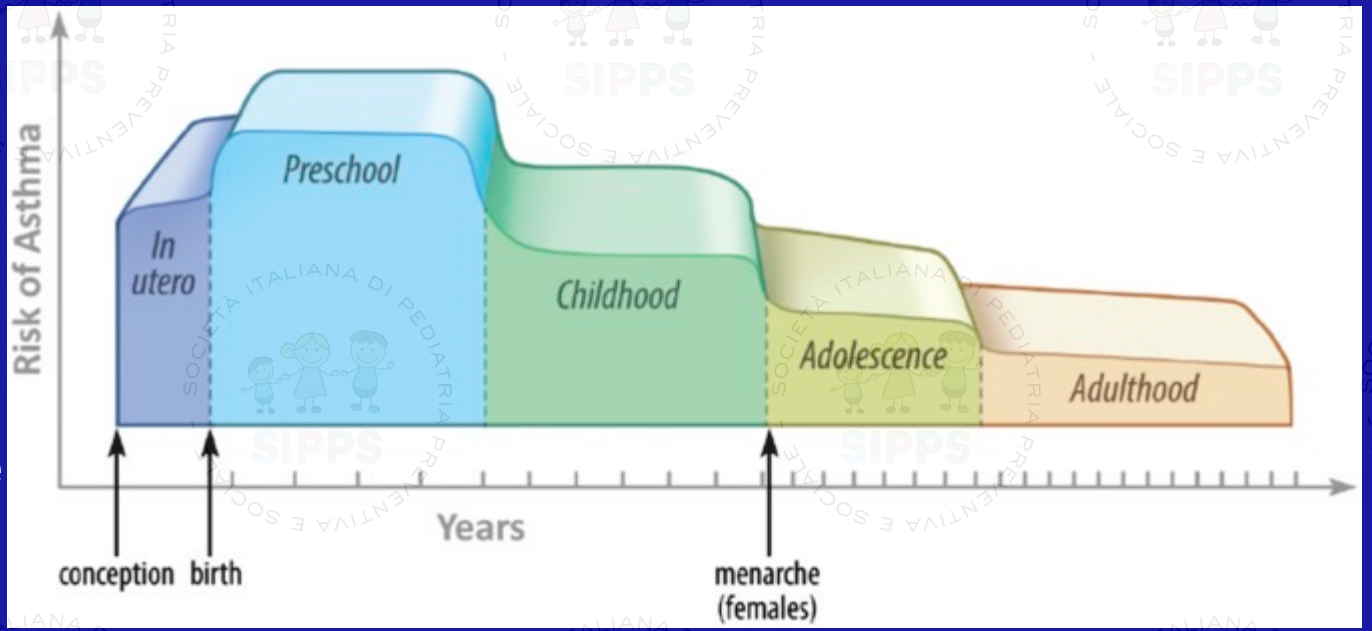
NHLBI WORKSHOP 2014

Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

Daniel J. Jackson[1], Tina V. Hartert[2], Fernando D. Martinez[3], Scott T. Weiss[4], and John V. Fahy[5]

Interventions in

Early postnatal life



- Viruses prophylaxis
- Immune modulation

Immunostimulants
Probiotics

Interventions in

Early postnatal life

↓

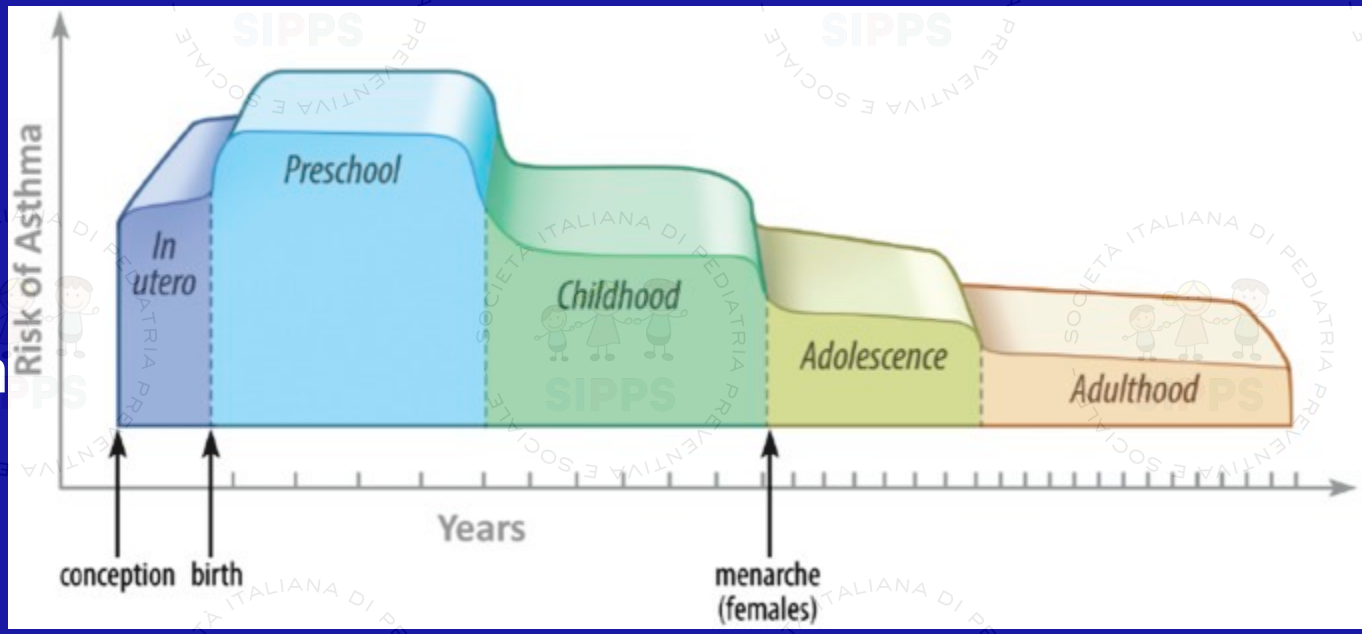
Immune modulation

↓

The rationale is

Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases *Ann ATS 2014*

Daniel J. Jackson[1], Tina V. Hartert[2], Fernando D. Martinez[3], Scott T. Weiss[4], and John V. Fahy[5]



Dendritic cell maturation

↓

↑ expression of TLR e class II HLA on dendritic cell surface

↓

IL1, IL6 & IL12 synthesis

↓

T lymphocites differentiation → Th_1

Pidotimod & wheezing and asthma

Efficacy and Safety of Pidotimod in Childhood Wheezing: A Pilot Study

90 ch (4.7±1.6 yrs) with recurrent [illegible] (*R* [illegible] *grainfluenzae*)

T0: PDT 400 m
T3 (3 mo o
T6 (6 mo

Treatment of recurrent viral wheeze with PDT results in a reduction in the n^ of patients requiring ED visits and/or hospitalization as well as the n^ of patients taking drugs (SABA; ICS; AB).

In the follow-up, once PDT was suspended, the number of patients with ≥ 1 episodes of wheeze and of those taking antibiotics further reduced.

N.*					.001
					n.s.
				/90	n.s.
				8/90	<0.05
N. of				4/90	n.s.
N. of patient		7/90	<0.05	4/90	n.s.

Manti, Curr Respir Med Rev 2021

Pidotimod & wheezing and asthma

Pidotimod decreases the *in vitro* exp… of CD… ripheral blood mononuclear c… dren.

PDT → i…
Periph…

CD30: type I transmembrane protein, member of TNF family

Associated with

- production of Th2 cytokines by CD4+ and CD8+ T-cells
- Th-2 disorders (atopic dermatitis; functional significance ?)

Down-regulation of CD30 → PDT as antiallergic?

- …

- No differenc… asthmatic subjects in terms of cyt… production (mild asthma? small sample…

Pidotimod: non solo IRR

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Pidotimod & PFAFA

Proposal for a new therapeutic high dose of Pidotimod in children with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome: a RCT.

PDT → new potential treatment in PFAPA syndrome for its immunodulatory effects?

22 ch with PFAPA syndrome randomly allocated to treatment with
PDT (800 mg/d) + betamethasone (0.5–1 mg on need on parents decision)
Betamethasone (0.5–1 mg on need on parents decision)

Phase 1: PDT + Bethametasone (3 mo)

Switch to

Phase 2: Bethametasone (3 mo)

Outcome parameters

N^ of episodes of fever, pharyngitis, aphthous stomatitis
Additional use of betamethasone on need.

Safety and tolerability: n^ and type of AEs

Manti, IJP 2020

Pidotimod & PFAFA

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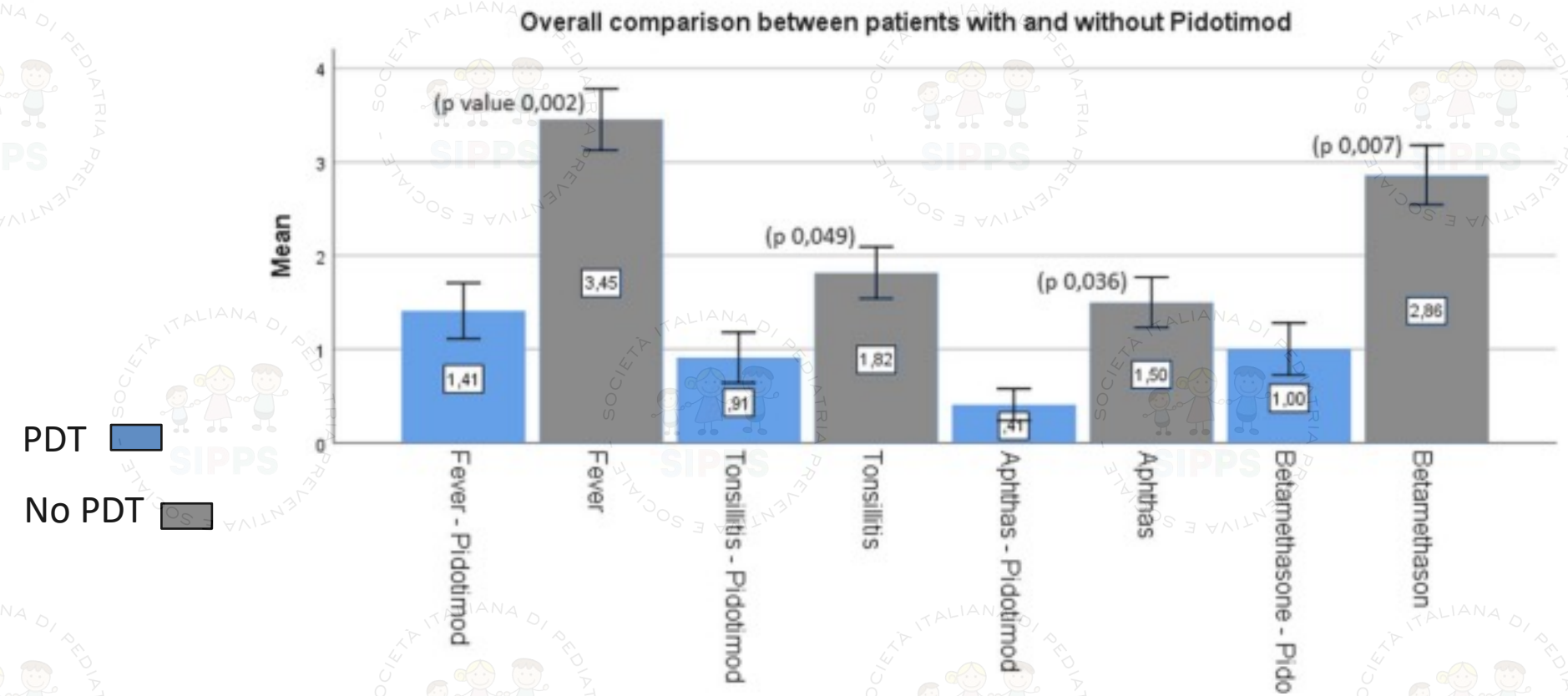


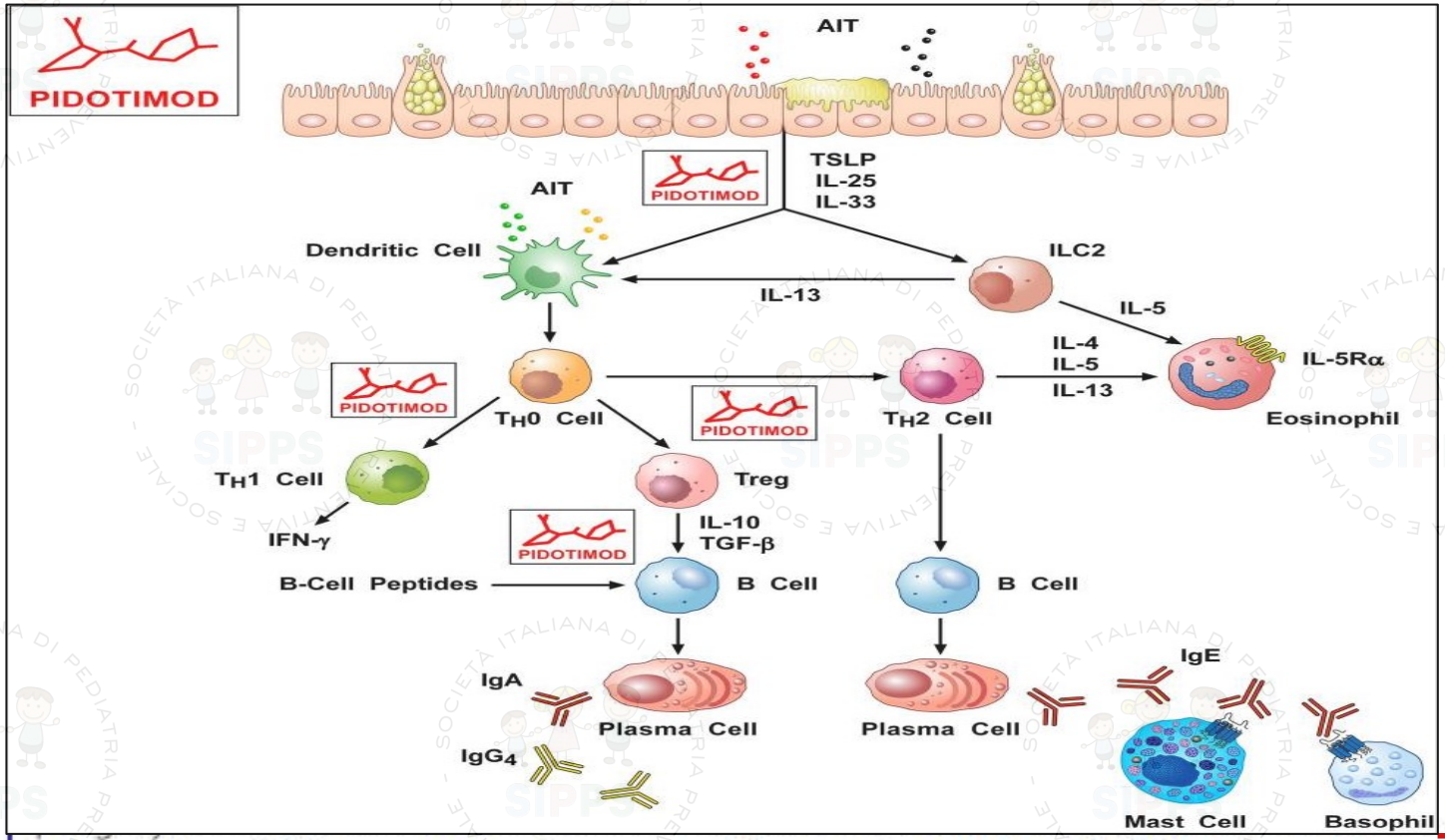
PDT is effective and safe to reduce PFAPA symptoms/signs
Although PDT does not change the natural history of disease, it significantly decreases the severity disease

Manti, IJP 2020

Pidotimod: non solo IRR

Conclusions

Puggioni, Multidisciplinary Respiratory Medicine (2019)



All these activities are potentially useful for several respiratory conditions such as asthma, COPD, and recurrent respiratory tract infections.