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Torino
10-12 ottobre 2024

RINOSINUSITE CRONICA: QUALI TERAPIE

A cura di

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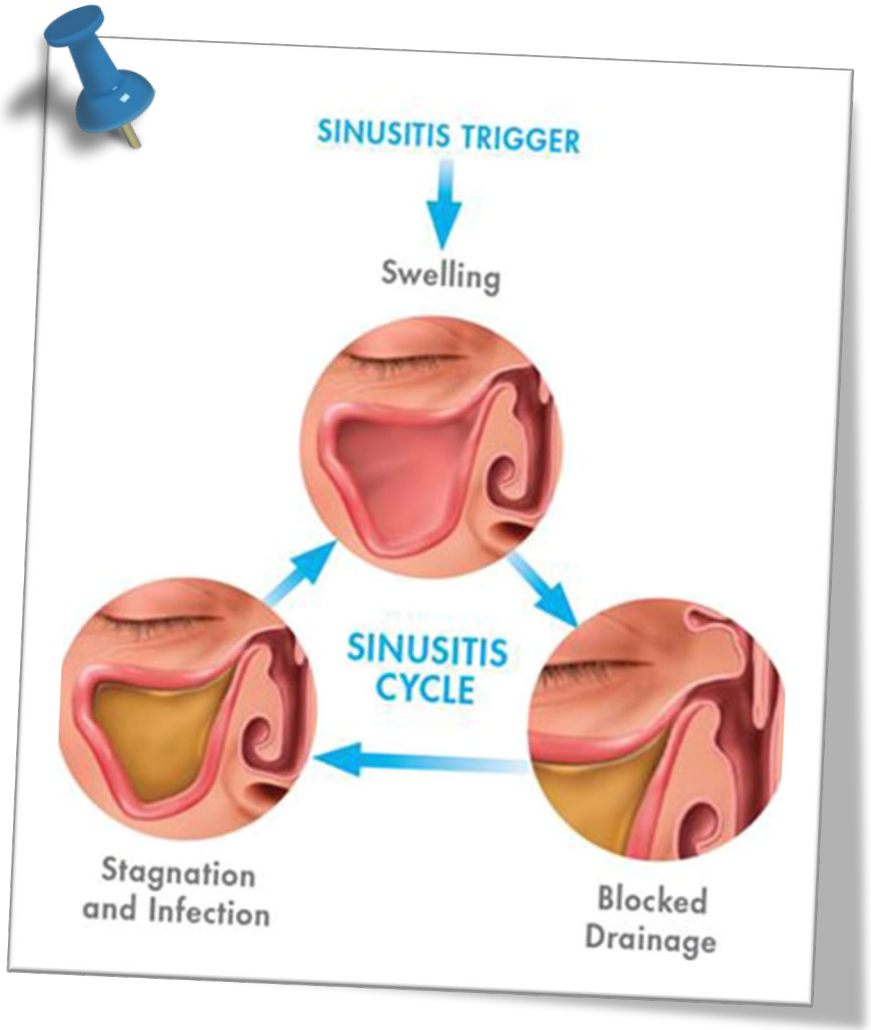
DEFINIZIONE CLINICA IN ETÀ PEDIATRICA



Rinosinusite = infiammazione del naso e dei seni paranasali, 2 o più sintomi:

- **ostruzione nasale / congestione o scolo nasale** (nasale anteriore / posteriore):
  - ± dolore facciale
  - ± tosse

e

- **segni endoscopici** di:
  - poliposi nasali e / o
  - secrezione mucopurulenta (meato medio)

e / o

- **edema / ostruzione della mucosa (meato medio)**

e / o

- **Modifiche CT:**
  - alterazioni della mucosa all'interno del complesso ostiomeatale e / o dei seni

RINOSINUSITE ACUTA (ARS)

<12 settimane

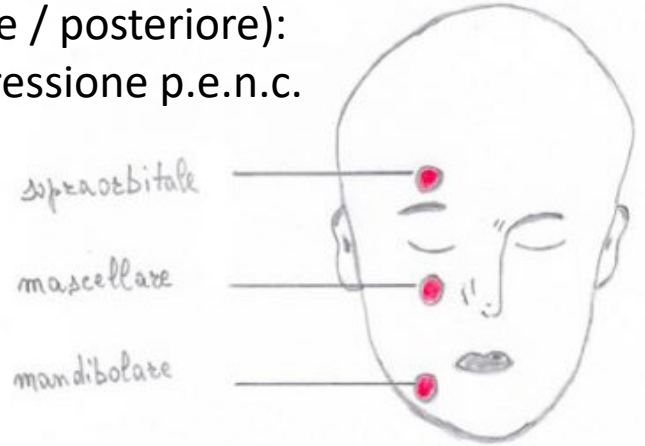
- blocco nasale / ostruzione / congestione
- o secrezione nasale limpida
- o tosse (diurna e notturna)

Indagare sintomi allergici (es. starnutazione, rinorrea acquosa, prurito nasale e prurito oculare)

RINOSINUSITE CRONICA (CRS)

≥12 settimane

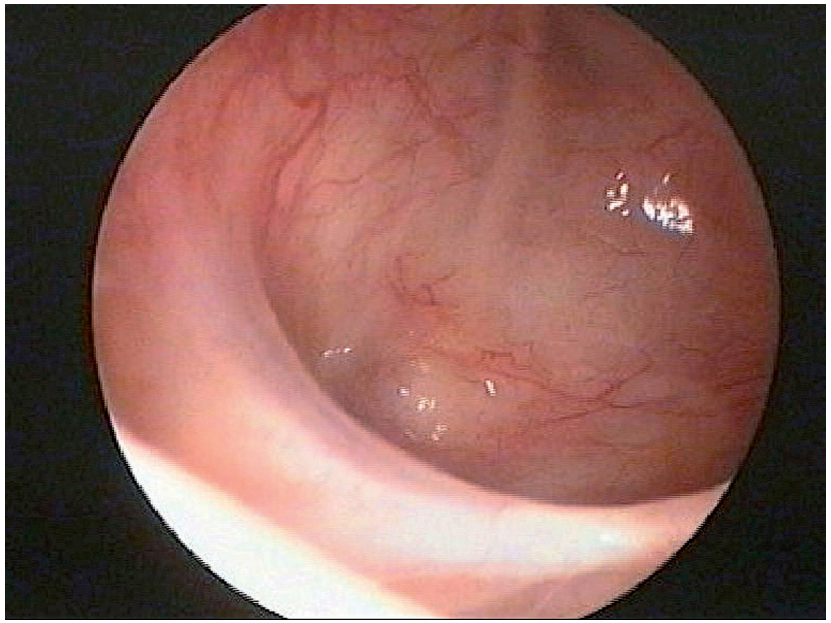
•blocco nasale / ostruzione / congestione/secrezione nasale (scolo nasale anteriore / posteriore):
- ± dolore facciale/ pressione p.e.n.c.
- ± tosse;



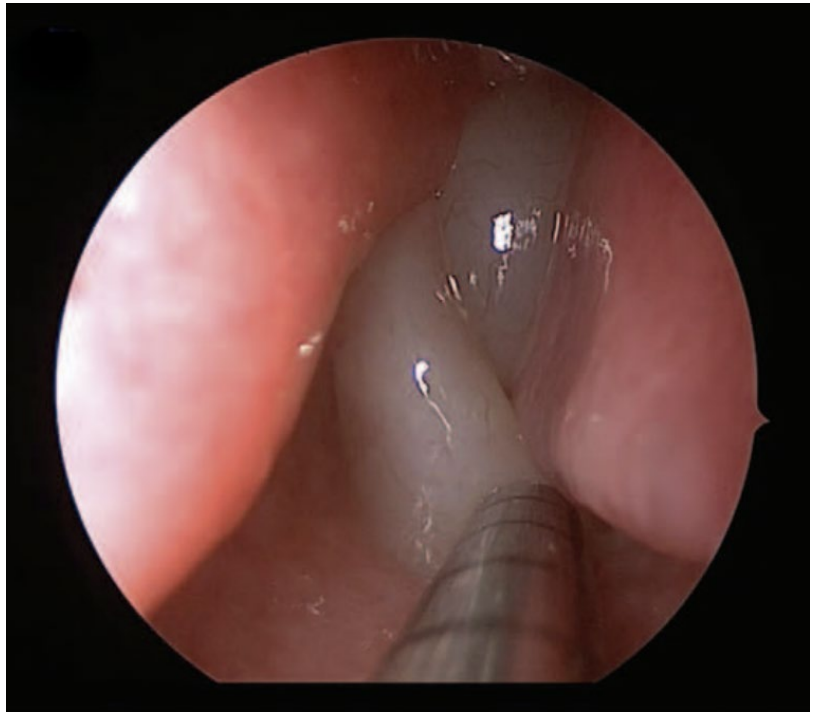
RINOSINUSITE ACUTA RICORRENTE (RARS)

ARS ≥ 4 episodi all'anno con intervalli liberi da sintomi

RINOSINUSITE CRONICA SENZA POLIPI (CRSsNP)



RINOSINUSITE CRONICA CON POLIPI (CRSwNP)

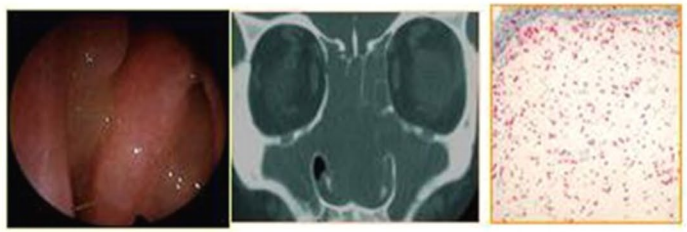


Ghent Classification of Chronic Rhinosinusitis

CRSsNP

Fibrosis, TGF-beta upregulation,
Th1 bias

CRSwNP



Edema, TGF-beta down-regulation,
lack of T regulatory cells

IL-5 endotype

IL-5 expression, eosinophilia

IFN/IL-17
expression,
neutrophilia

Staphylococcal
enterotoxins (SE)

SE-IgE endotype

SE-IgE expression,
total IgE increased,
severe eosinophilia

No SE-IgE expression

HIGH

Risk for co-morbid asthma
and repeated surgery

LOW

J Allergy Clin Immunol. 2017 Dec;140(6):1705-1708.e3. doi: 10.1016/j.jaci.2017.07.031. Epub 2017 Sep 1.

Serum periostin, IgE, and SE-IgE can be used as biomarkers to identify moderate to severe chronic rhinosinusitis with nasal polyps

Karin Jonstam [1], Marit Westman [2], Gabriële Holtappels [3], Cecile T J Holweg [4], Claus Bachert [5]

TABLE I. Median concentrations and IQR of inflammatory markers in serum and tissue among patients with CRSwNP, patients with CRSsNP, and controls, and the proportion of patients expressing these inflammatory markers above cutoff in serum and tissue

Parameter	CRSwNP	CRSsNP	Controls	*P* value	CRSwNP vs CRSsNP (*P* value)	CRSwNP vs controls (*P* value)	CRSsNP vs controls (*P* value)
Serum concentration, median (IQR)							
Periostin (ng/mL)	68.9 (57.1-86.6)	53.5 (46.4-64.3)	56.0 (48.3-67.8)	<.0001*	<.0001†	<.0001†	>.05†
IgE (kU/L)	84.5 (36.2-231.4)	44.4 (16.1-113.5)	50.1 (13.4-131.5)	<.001*	<.001†	<.01†	>.05†
SE-IgE (kUA/L)	0.13 (0-0.43)	0.07 (0-0.23)	0.08 (0-0.23)	<.0001*	<.001†	<.0001†	>.05†
ECP (μg/L)	15.3 (7.7-28.9)	13.1 (6.8-21.6)	11.2 (5.5-18.9)	<.01*	<.01†	<.01†	>.05†
sIL-5Rα (pg/mL)	318.5 (205.9-527.6)	239.4 (171.3-363)	219 (142.8-300.4)	<.0001*	<.001†	<.0001†	>.05†
Proportion of patients above cutoff (numbers) in serum, % (n/N)							
Periostin > 48.5 ng/mL	93 (129/138)	72.7 (80/110)	75 (78/104)	<.0001‡	<.0001§	<.0001§	>.05§
IgE >96 kU/L	44.4 (64/144)	28.4 (35/123)	30 (33/110)	<.05‡	<.01§	<.05§	>.05§
SE-IgE >0.28 kUA/L	33.3 (48/144)	26 (32/123)	22.7 (25/110)	>.05‡	>.05§	>.05§	>.05§
Tissue concentration, median (IQR)							
IgE U/g tissue	203.2 (72.1-529.7)	25.2 (7.3-76.6)	8.9 (1.9-22.3)	<.0001*	<.0001†	<.0001†	<.01†
IL-5 pg/g tissue	132.3 (23.9-519.5)	0 (0-17.5)	0 (0-0)	<.0001*	<.0001†	<.0001†	<.0001†
ECP μg/g tissue	4.626 (2.2-9.4)	0.85 (0.20-2.3)	0.11 (0.07-0.35)	<.001*	<.0001†	<.0001†	<.0001†
Proportion of patients above cutoff (numbers) in tissue, % (n/N)							
IgE >0.35 U/g tissue	97.3 (110/113)	87.2 (82/94)	71.9 (64/89)	<.0001‡	<.01§	<.0001§	<.05§
SE-IgE >0.35 UA/g tissue	20.3 (23/113)	3.2 (3/94)	0 (0/92)	<.0001‡	<.001§	<.0001§	>.05§
IL-5 >6.6 pg/g tissue	83.9 (94/112)	32.3 (30/93))	2.4 (2/84)	<.0001‡	<.0001§	<.0001§	<.0001§

ECP, Eosinophil cationic protein; *IQR*, interquartile range.
*Kruskall-Wallis test.
†Mann Whitney *U* test.
‡Chi-square test.
§Fisher exact test.

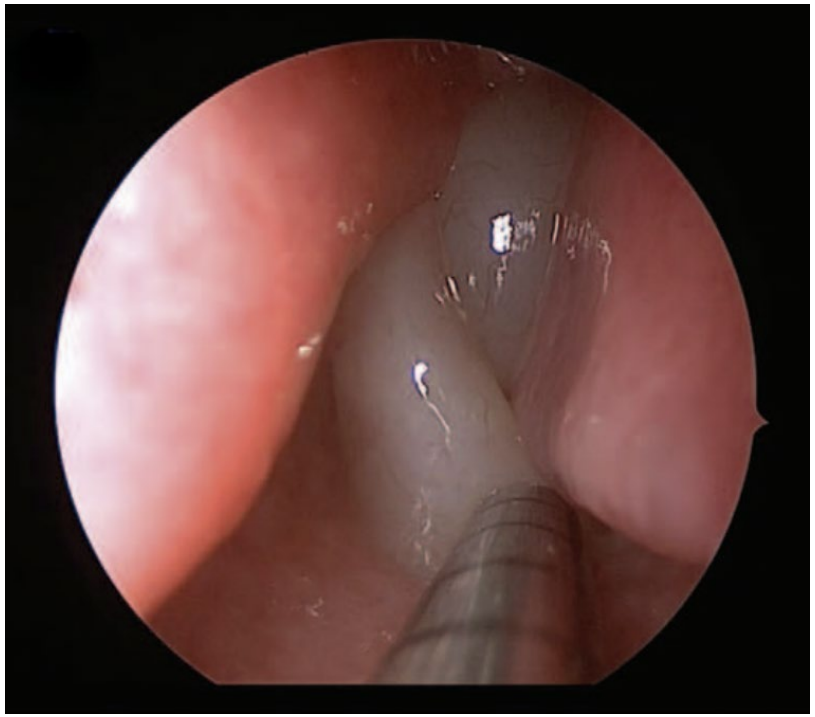
SE-IgE sierica: SE-IgE è legata alle enterotossine di Staphylococcus aureus che agiscono come superantigeni, promuovendo un'infiammazione più grave nei pazienti con CRSwNP.

Periostina sierica: (indotto da IL4, IL5 e IL13) è significativamente elevato nei nelle CRSwNP rispetto ai CRSsNP o ai CTRL.

Questi biomarker possono identificare pazienti con CRSwNP moderata o grave, riducendo la necessità di biopsie

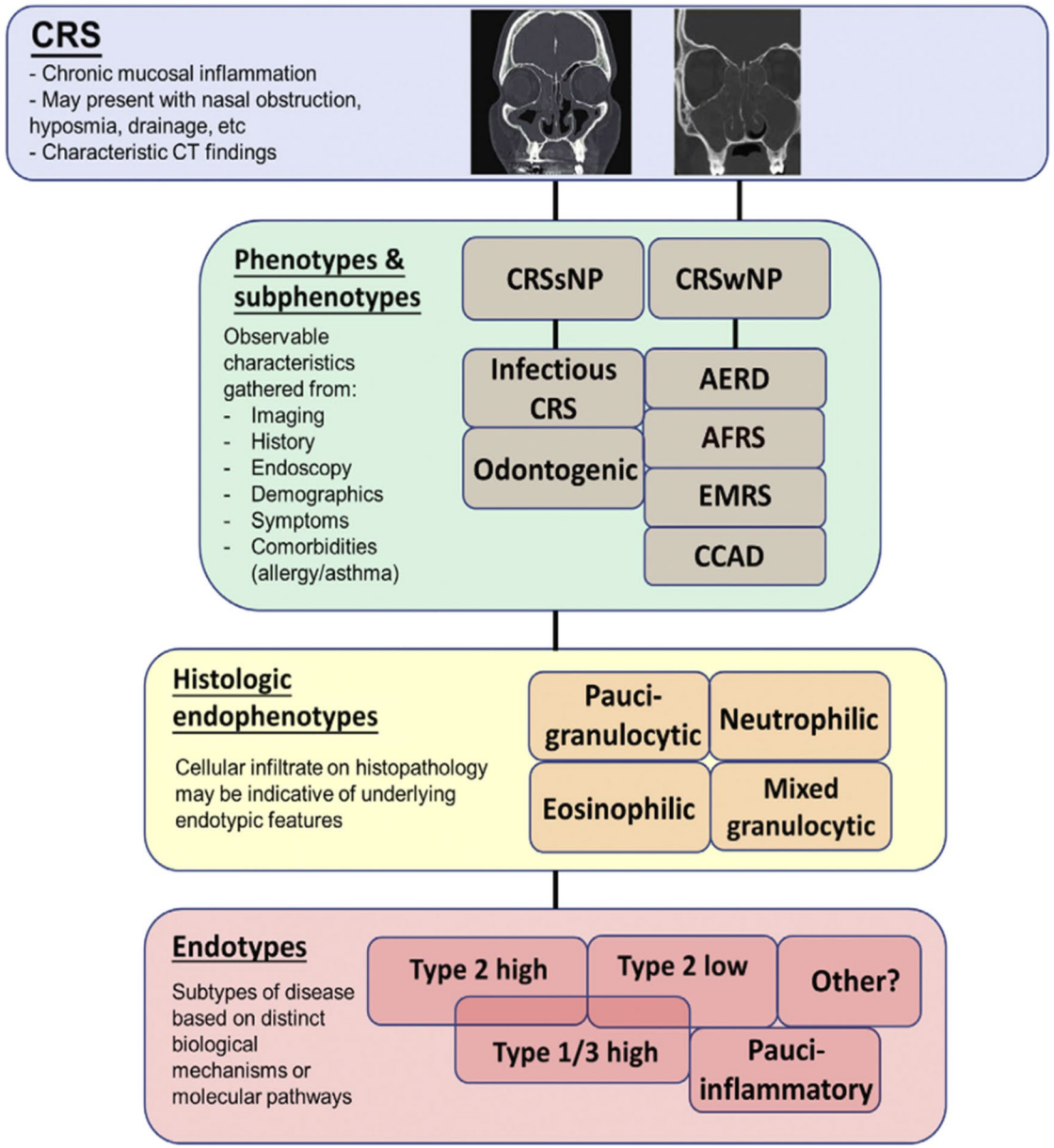
Inoltre, i livelli di periostina, IgE e SE-IgE nel siero possono anche suggerire la risposta a trattamenti come corticosteroidi e biologici.

RINOSINUSITE CRONICA CON POLIPI (CRSwNP)



FENOTIPI

1. **CRSwNP con elevati livelli di SE-IgE**
2. **CRSwNP con elevati livelli di periostina**
3. **CRSwNP eosinofilico con elevati livelli di IgE totali**
4. **CRSwNP con predominanza Th1/Th17**: infiammazione **neutrofilica**, resistente ai corticosteroidi, e ai trattamenti biologici per le citochine Th2.

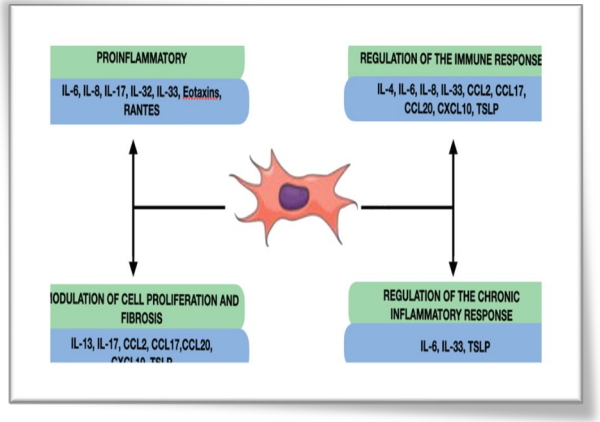


- **CRSsNP**: Rinosinusite cronica senza polipi nasali.
- **CRSwNP**: Rinosinusite cronica con polipi nasali.
- **AERD**: Aspirin-exacerbated respiratory disease.
- **AFRS**: Allergic fungal rhinosinusitis.
- **EMRS**: Eosinophilic mucin rhinosinusitis.
- **CCAD**: Chronic cough-associated disease.

…CRSwNP prima della comparsa dei polipi è una CRSsNP…

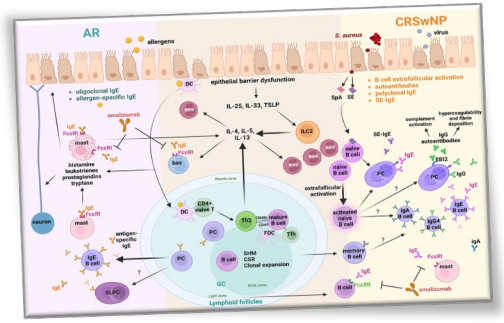
1 INFIAMMAZIONE CRONICA

- Tre diversi endotipi infiammatori T1, T2 e T3.
- 19 diverse citochine prodotte dai NPDF



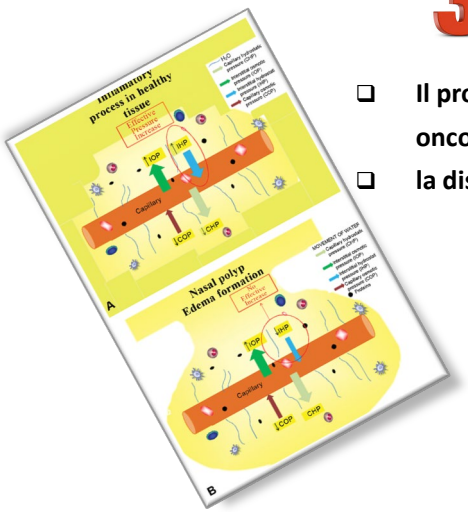
2 DISREGOLAZIONE IMMUNITARIA

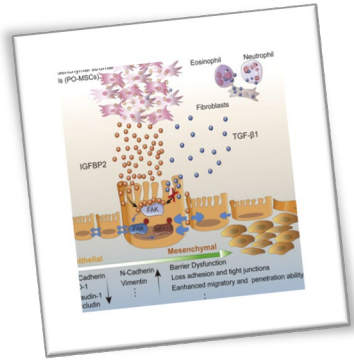
- Infiltrazione dei linfociti B e dei plasmablasti
- ↑ ab tissutali: IgG1, IgG2, IgG4, IgM, IgA1, IgA2 e IgE



3 DISFUNZIONE MECCANICA

- **Il processo infiammatorio mantiene la pressione oncotica facilitando la perdita di volume dai capillari**
- **la disfunzione meccanica ostacola il ritorno venoso**

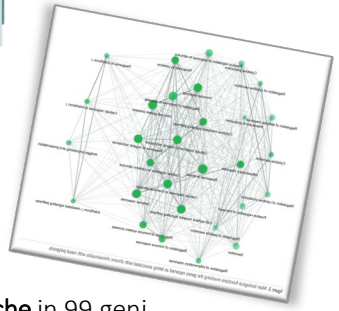




4 DISFUNZIONE EPITELIALE

- **Espansione delle cellule basali, chemiosensoriali**: (cellule tuft, brush e solitarie), **ciliate (fibrosi cistica) cellule neuroendocrine polmonari** e **Perdita dell'epitelio ghiandolare**

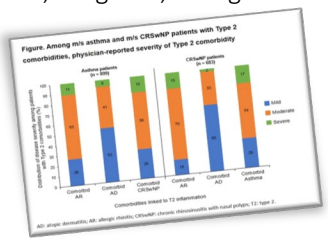
5 GENETICA ED EPIGENETICA



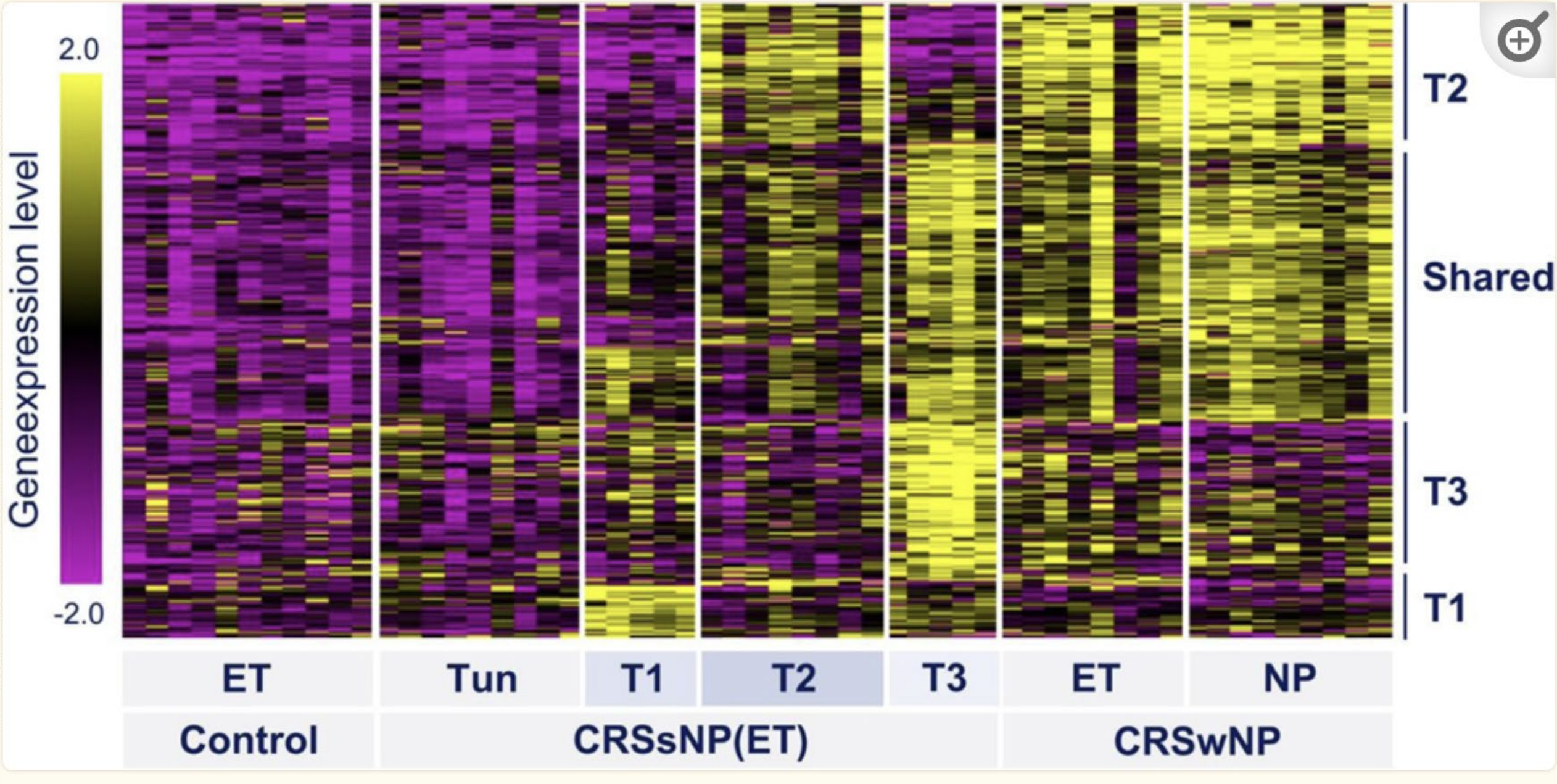
- CRSwNP, più di **150 varianti genetiche** in 99 geni, organizzati in **8 reti principali**
- **Meccanismi epigenetici**: i**(miRNA)** giocano un ruolo chiave (identificati **87 miRNA**)

6 COMORBIDITÀ

- **Fibrosi cistica:** infiammazione neutrofilo/Th17
- **AERD:** Th2, aumentato IFN-γ da parte degli eosinofili (Th1)
- **Immunodeficienze/ Disfunzioni immunologice (IgG4 RD)**
- **Rinosinusite fungina allergica (AFRS)**: Th2
- **forme specifiche** (sarcoidosi, Wegener, Churg-Strauss)
- **Rinite allergica/ Asma**

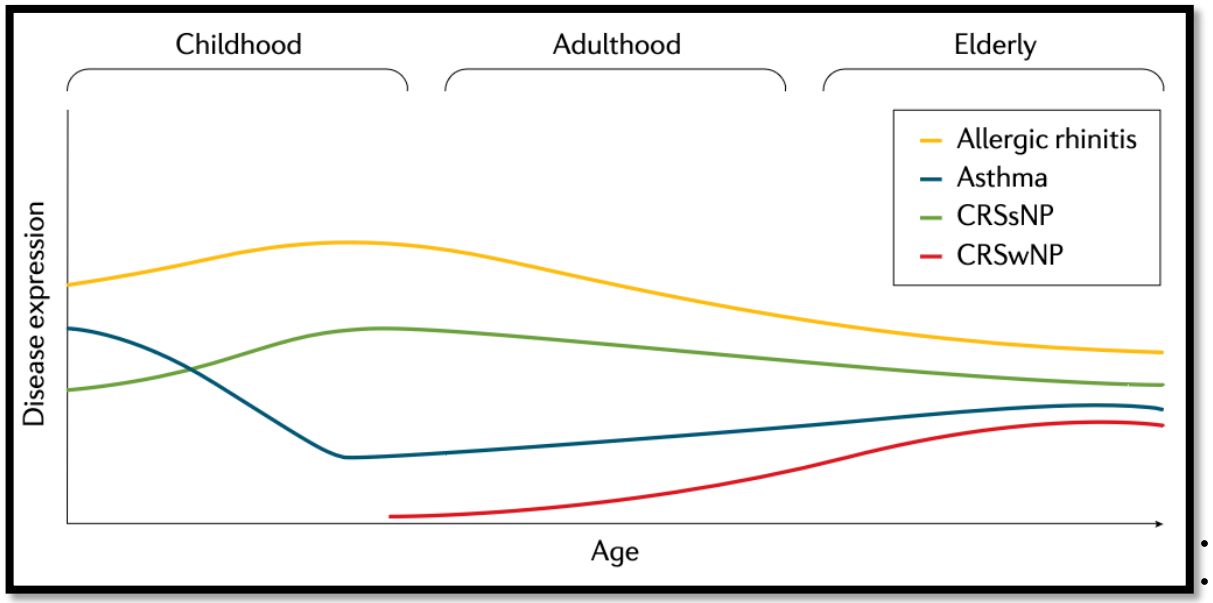


Endotipo	Fenotipo	Caratteristiche biologiche	Condizioni associate	Trattamento consigliato
Th2 (CRS tipo 2)	CRSwNP	- ↑↑↑ **IL-4**, **IL-5**, **IL-13** - ↑↑↑ **IgE** e **eosinofili** - Biomarcatori: **Periostina**, **SE-IgE**	- Poliposi nasale - Asma - Sensibilità all'aspirina (NSAID-ERD)	- Corticosteroidi - Biologici (anti-IL-5, anti-IgE) (es. **mepolizumab**, **omalizumab, dubilupam**)
Th1/Th17 (CRS tipo 1)	CRSsNP	- ↑↑↑**IFN-γ** (Th1), **IL-17** (Th17) - ↑↑↑ **neutrofili**	- Più comune in CRS senza polipi - Spesso non allergico	- Meno responsivo ai corticosteroidi - Antibiotici - Biologici? (Anti-IL17, anti-IL21, anti-IFNg?) - Chirurgia per i casi resistenti
Non Th2/non eosinofilico	CRSsNP e CRSwNP	- ↑↑↑ **neutrofili** senza Th2	- Più comune in popolazioni asiatiche - Infiammazione meno eosinofilica	- Antibiotici - Chirurgi


2.0
Geneexpression level
-2.0
T2
Shared
T3
T1
ET
Tun
T1
T2
T3
ET
NP
Control
CRSsNP(ET)
CRSwNP

Epidemiologia dell'CRS in pediatria

- La prevalenza è inferiore rispetto agli adulti
- 2-5% della popolazione pediatrica.
- I tassi possono variare in base alla regione geografica, ai fattori ambientali, e alla presenza di condizioni predisponenti come allergie o anomalie anatomiche.
- Prevalenza maggiore dell'ARS tra i 10 e 15 che aumenta progressivamente
- Dati epidemiologici scarsi e datati, la maggior parte degli studi pubblicati si riferiscono a bambini con malattie sistemiche sottostanti.

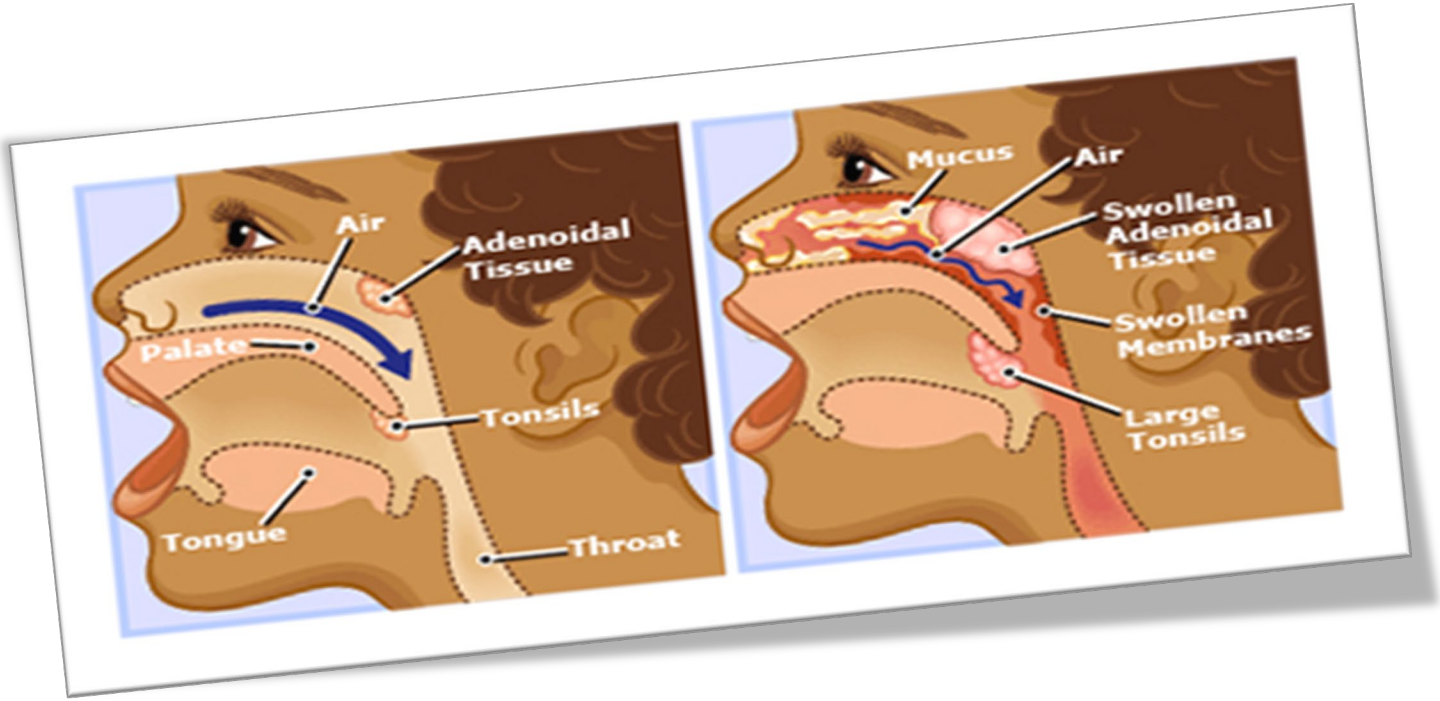


Inflammation/Infections	Systemic Diseases
Recurrent upper respiratory tract infections	Cystic fibrosis
Developing immune system	Primary ciliary dyskinesia
Adenoid hypertrophy	Immunodeficiencies
Allergic and non-allergic rhinitis	Vasculitis
Tobacco smoke exposure	
Environmental pollution	
Gastro-esophageal reflux disease	

1. Gilani S. et al. Chronic Rhinosinusitis in Children: Pathophysiology, Evaluation, and Medical Management. 2018
2. Zachariah C. et al. Clinical Guidelines on Chronic Rhinosinusitis in Children. 2019
3. Hopkins, Claire. "Chronic Rhinosinusitis with Nasal Polyps." 2019
4. Di Cicco et al..Nasal Polyps in Children: The Early Origins of a Challenging Adulthood Condition. 2021

FATTORI PREDISPONENTI CRS

- ARS ?
- Fattori anatomici
- Allergia
- Fumo passivo
- RGE ?
- Alterata funzionalità ciliare



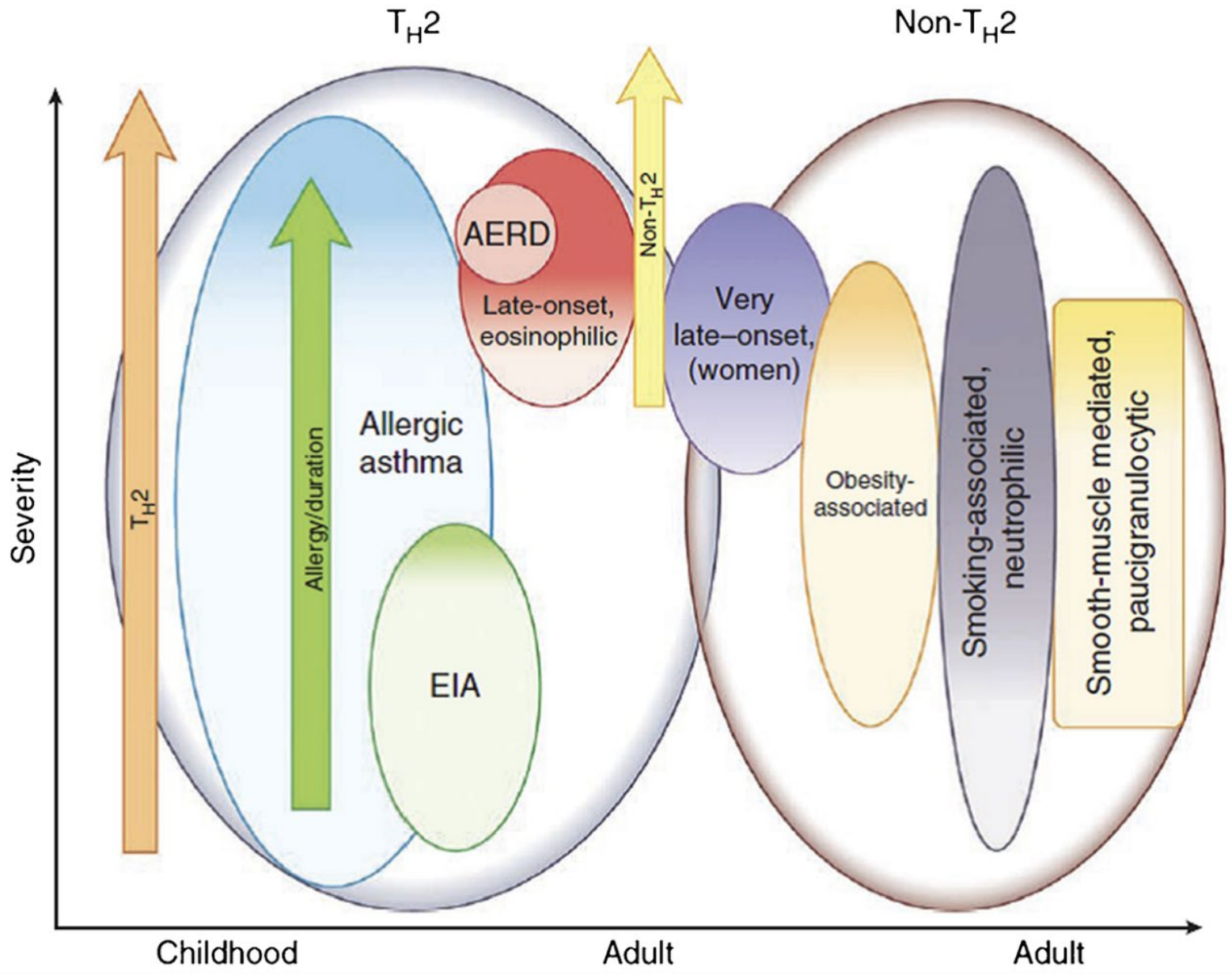
- **IPERTROFIA ADENOIDEA**

- **Immunodeficienze umorali (SIgAd e sottoclassi IgG)**

Bassi livelli di Ig G, Ig A e Ig M rispettivamente nel 18%, 17% e 5%

- **ASMA**

FATTORI PREDISPONENTI CRS



RSC e ASMA

Respiratory Medicine 141 (2018) 94–99

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hort review

ediatric rhinosinusitis and asthma

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RTICLE INFO

ywords:
thma
inosinusitis
sal polyposis
sinophil
sophil
5

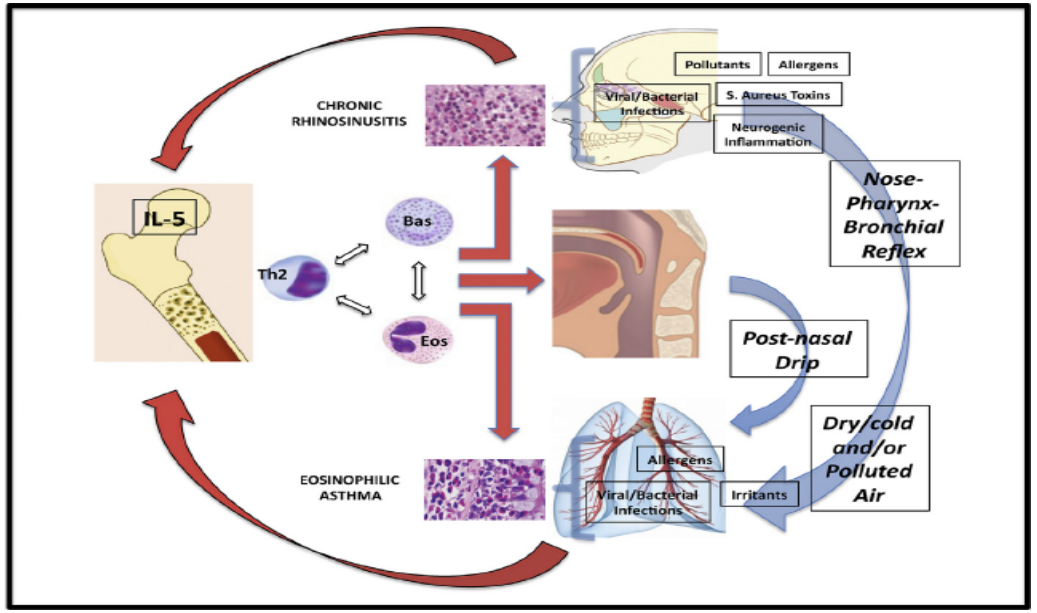
ABSTRACT

Both asthma and rhinosinusitis are complex and heterogeneous diseases and, importantly, they often coexist: these diseases can be concomitant in 35–65% of affected children, according to different studies. Thus, evaluating this comorbidity in the clinical practice should be paramount. In this review, we focused our discussion on the multiple pathophysiological aspects that may link rhinosinusitis and asthma in the pediatric population. Although rhinosinusitis may exacerbate asthma through several mechanisms occurring by contiguity, actually this aspect seems to be only one component of the complex interplay between upper and lower airways. In particular, the onset of an important and persistent Th2-driven inflammatory process dominated by eosinophils presence at one site of the airways, may release into the bloodstream several cytokines; in their turn, those can lead to the stimulation of the bone marrow, which may function as a systemic amplifier of such an eosinophilic inflammation.

- 40% dei pz con asma ha anomalie dei seni paranasali
- nei pz con CRS, l'asma doppia etiopatogenesi:
  - contiguità della mucosa
  - infiammazione eosinofilica (> CRS+asma vs CRS)
- i pz con asma non controllato sono più a rischio di RSC

… infiammazione Th2 ed eosinofilica + citochine

… midollo osseo che amplifica l'infiammazione eosinofilica



SVILUPPO DEI SENI PARANASALI

SENO	INIZIO SVILUPPO	TERMINE SVILUPPO
ETMOIDALE	Presente alla nascita	4-6 anni
MASCELLARE	4-6 mesi	4-6 anni
FRONTALE	2 anni	8-10 anni
SFENOIDALE	3-5 anni	12-14 anni

Current Allergy and Asthma Reports (2019) 19:14
https://doi.org/10.1007/s11882-019-0845-7

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Clinical Guidelines on Chronic Rhinosinusitis in Children

Zachariah Chandy[1] · Elisabeth Ference[2] · Jivianne T. Lee[1]

Table 1 Evidence-based recommendations regarding medical and surgical treatment of pediatric chronic rhinosinusitis (CRS)

Therapy	Recommendation	Level of evidence
Nasal saline spray	• First-line treatment option.	• Well supported in current literature.
Nasal steroid spray	• First-line treatment option.	• Although limited evidence in pediatric population, given relative effectiveness and limited risk demonstrated in adult population, nasal steroid stray is recommended in the pediatric population
Antibiotic irrigation	• No consensus at this time. • May be most useful following endoscopic sinus surgery.	• Limited evidence analyzing risks and benefits at this time.
Oral antibiotics	• First-line treatment option. • Amoxicillin, amoxicillin/clavulanate, or cephalosporin are recommended as first line. • Clindamycin recommended for anaerobes. • For penicillin-allergic patients, dual therapy with third-generation cephalosporin and clindamycin or levofloxacin is recommended. • Duration of therapy: no consensus, however, 20 days is superior to 10 days.	• There is limited evidence in current literature regarding pediatric CRS specifically. These recommendations are mainly extrapolated from studies analyzing benefits seen in pediatric ARS.
Intravenous antibiotics	• No utility for routine pediatric CRS. • Indicated for intraorbital or intracranial complications of CRS.	• Limited evidence for routine pediatric CRS. Utility is well supported when complications of CRS are present.
Adenoidectomy	• First-line surgical option if failed medical therapy.	• Well supported in current literature.
Balloon sinuplasty	• No consensus at this time.	• Although safety profile is well supported, limited evidence demonstrating benefit at this time.
Endoscopic sinus surgery	• First-line surgical option with or without adenoidectomy if failed medical therapy. • Indicated if patient has anatomic obstructing lesions, nasal polyps, or if patient has comorbidities such as cystic fibrosis, primary ciliary dyskinesia, or immunodeficiencies.	• Well supported in current literature.

La diagnosi di RSC in età pediatrica è principalmente basata sui sintomi clinici e supportata se necessario dall'endoscopia nasale e dalla CT

History:

3 months of **at least 2** of the following symptoms **purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough**

Nasal Endoscopy:

Nasal endoscopy should be attempted in the pediatric population to look for **mucosal edema, purulent drainage or nasal polyps** to establish the diagnosis of CRS

Imaging:

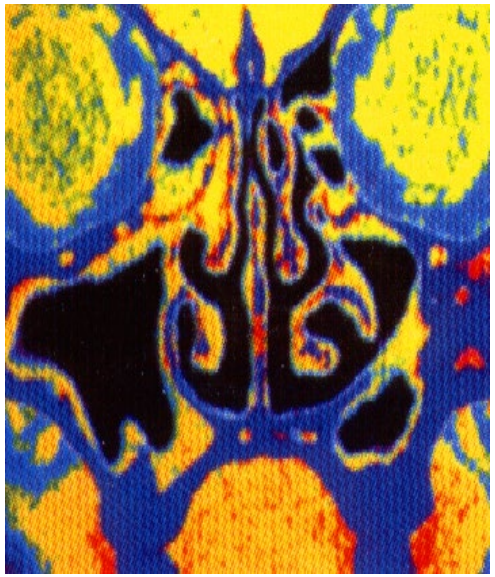
CT is the initial imaging modality of choice. CT showing **ostiomeatal complex or sinus edema** can establish the diagnosis of CRS.

MRI is indicated if there is concern for **intracranial or intraorbital complications of sinusitis**

Cultures:

Endoscopically guided middle meatal cultures are indicated if patients have **NOT responded to empiric therapy within 72 hours, have significant comorbidities, or have severe illness**

DIAGNOSTICA PER IMMAGINI



RX standard non è indicata:

- non consente la visualizzazione del complesso ostio meatale (COM) e del recesso sfeno-etmoidale (RSE)
- visualizza in modo inadeguato l'etmoide e lo sfenoide

TC dei seni paranasali deve essere riservata ai casi di RSA :

- complicata
- persistente e/o non rispondente al trattamento medico
- ricorrente/cronica

RMN indicata per definizione dei tessuti molli in casi di:

- complicanze orbitali e/o extraorbitali (intracraniche)

Esposito S. Pediatr Allergy Immunol 2007

DIAGNOSI MICROBIOLOGICA

GOLD STANDARD:
aspirato dei seni paranasali con conta delle colonie batteriche (+ se ≥ 10^4CFU/ml)

<u>MOLTI SVANTAGGI:</u>
- Invasiva
- Dolorosa
- Attuabile solo da specialisti

….*non utilizzabile nella pratica clinica routinaria*

PS: indicata in pazienti immunocompromessi e in casi non responsive a terapia

Review > Curr Allergy Asthma Rep. 2019 Feb 22;19(2):12. doi: 10.1007/s11882-019-0850-x.

Precision Medicine in Rhinosinusitis

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Affiliations + expand

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Abstract

Purpose of review: Our scope is the presentation of research and clinical progresses in relation to precision medicine that are expected to alter our clinical practice in relation to chronic rhinosinusitis (CRS). Current knowledge on phenotypes and endotypes, biomarkers, and clinical markers for diagnosis, medical and surgical therapy, and prognosis is presented as well as the role of precision medicine in United Airway Disease and SCUAD (severe-uncontrolled chronic upper airway inflammation).

Recent findings: Current technological progresses, mostly in relation to molecular biology and information technology, have permitted more detailed pathophysiological assessments and multidimensional approaches in airways diseases. Based on the concept of united airways diseases, new classification schemes, called endotypes, have been proposed for CRS. In addition, novel biological treatments that have been introduced for the treatment of asthma show great promise as well for severe uncontrolled cases of CRS with nasal polyps. Central to this approach are new biomarkers that are being examined in relation to complex bio-clinical traits of CRS. As this narrative review of the aforementioned precision medicine initiatives in relation to CRS advances, a modification of current practice is expected not only for severe chronic upper airways diseases in tertiary centers but also for milder and more common cases that are being encountered in the community.

Table 1 Potential biomarkers in CRS and their reported relationship with specific phenotypes, endotypes, and treatment options

Biomarkers	Diagnosis (phenotypes/endotypes)	Treatment/ prognosis
Eosinophils	Type 2 immune reaction	Reboot surgery? GATA3 DNAzyme spray? Clarithromycin
IgE, SE-IgE	CRSwNP except AERD	Early monitoring of AIT (allergen immunotherapy) Omalizumab (anti-IgE)
Urine LTC_4 (cysteinyl leukotriene)	AERD	PGD_2 receptors antagonists, leukotriene receptor antagonists (i.e., montelukast and zafirlukast), 5-lipoxygenase inhibitor (i.e., zileuton), selective purinergic receptors P2Y12 (prasugrel), and T prostanoid receptors (ifetroban) antagonists.
IgG_4		AIT
Cytokines (IL-4, IL-5)		Monoclonal antibodies (biological, biosimilars) Long-term antibiotics

Precision Medicine (PM) per modificare la prognosi:

- fenotipi, endotipi, biomarkers, sintomi, terapia medica/chirurgica
- farmaci biologici per l'asma promettenti anche per CRSwNP

Table 3 The submucosal inflammatory cell of CRSsNP and CRSwNP by HE staining

	CRSsNP		CRSwNP			
	6-18 y (n=15)		6-12 y (n=24)		13-18 y (n=28)	
	Absolute value	proportion	Absolute value	proportion	Absolute value	proportion
Blood NEU	4.138±1.22	0.536±0.134	3.707±1.869	0.467±0.129	4.971±2.17	0.62±0.121
Blood EOS	0.046±0.05	0.006±0.005	0.041±0.026	0.005±0.003	0.027±0.021	0.004±0.003
Tissue EOS	11.514±15.279	0.093±0.135	14.93±18.087	0.131±0.162†	12.359±18.402	0.095±0.137
Tissue NEU	1.421±2.192	0.011±0.018	1.373±1.952	0.013±0.018	1.642±2.352	0.012±0.018

Table 4 The expression of Th1/Th2/Th17-related cytokines between pediatric CRSsNP and CRSwNP as per immunochemistry

	CRSsNP	CRSwNP	
	6-18 y (n=15)	6-12 y (n=24)	13-18 y (n=28)
IFN-γ	0.522±0.294	0.56±0.331	0.504±0.307
IL-4	0.023±0.011	0.068±0.104‡	0.044±0.039‡
IL-5	0.165±0.104	0.228±0.195†	0.131±0.083
IL-13	0.265±0.217	0.433±0.215†	0.321±0.209
IL-17	0.182±0.15	0.251±0.166†	0.116±0.079
IL-23	0.138±0.074	0.203±0.107†	0.15±0.08

Table 5 The tissue protein expression of Th1/Th2/Th17-related cytokines as per ELISA

	CRSsNP	CRSwNP		Controls
	6-18 y (n=11)	6-12y (n=11)	13-18 y (n=16)	6-18 y (n=10)
IFN-γ	39.5±21.7†	46.8±31.2‡	42.3±22.6‡	21.7±19.3
IL-4	-	59.7±18.5	54.6±12.8	-
IL-5	18.6±9.6	183.2±65.6†‡	133.9±58.5†‡	13.2±8.1
IL-13	168.9±41.5	278.6±76.3†	213.4±48.7†	-
IL-17	239.3±173.6‡	573.2±288.1†‡	146.8±101.9‡	48.9±11.5
IL-23	173.6±99.5	378.2±119.6†	211.3±108.5	-

The data were expressed as mean±SD
The protein concentrations are in pg/mL
†Compared with CRSsNP or 13-18 y CRSwNP, P <0.05
‡Compared with control, P <0.05
Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ELISA, enzyme-linked immunosorbent assay

- **CRSwNP** è caratterizzato da un'infiammazione mista **Th2/Th17** con una predominanza eosinofilica.

- **CRSsNP** è più dominato da una risposta **Th1/Th17**, associata a neutrofili e meno eosinofili.

Cho SH et al Phenotypes of Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2020.

Stadiazione e tool diagnostici

Tabella 1. Nasal polyp score (NPS)

Rilievi endoscopici (punteggio per ogni lato)
0 = no polipi
1= piccoli polipi nel meato medio/edema
2 = meato medio bloccato
3 = polipi che si estendono oltre il meato medio, senza una ostruzione completa oppure che si estendono al recesso sfeno-etmoidale
4 = poliposi nasale massiva

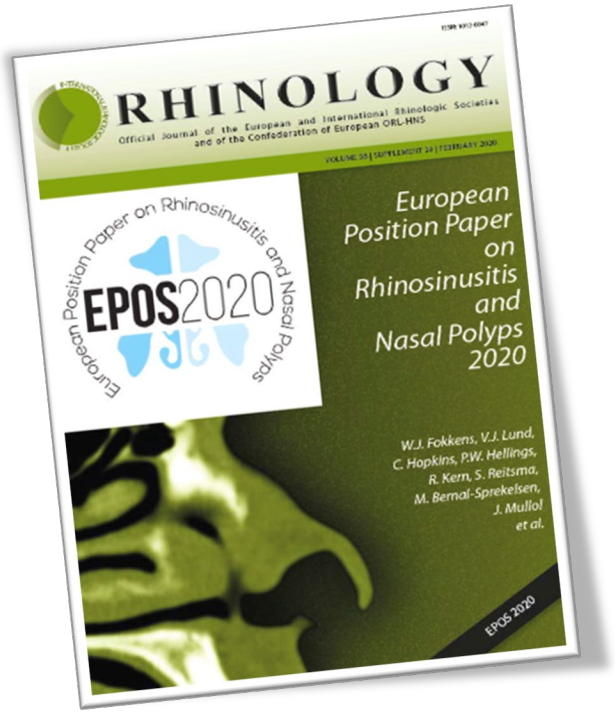
Tabella 2. Stadiazione TC Lund-Mackay

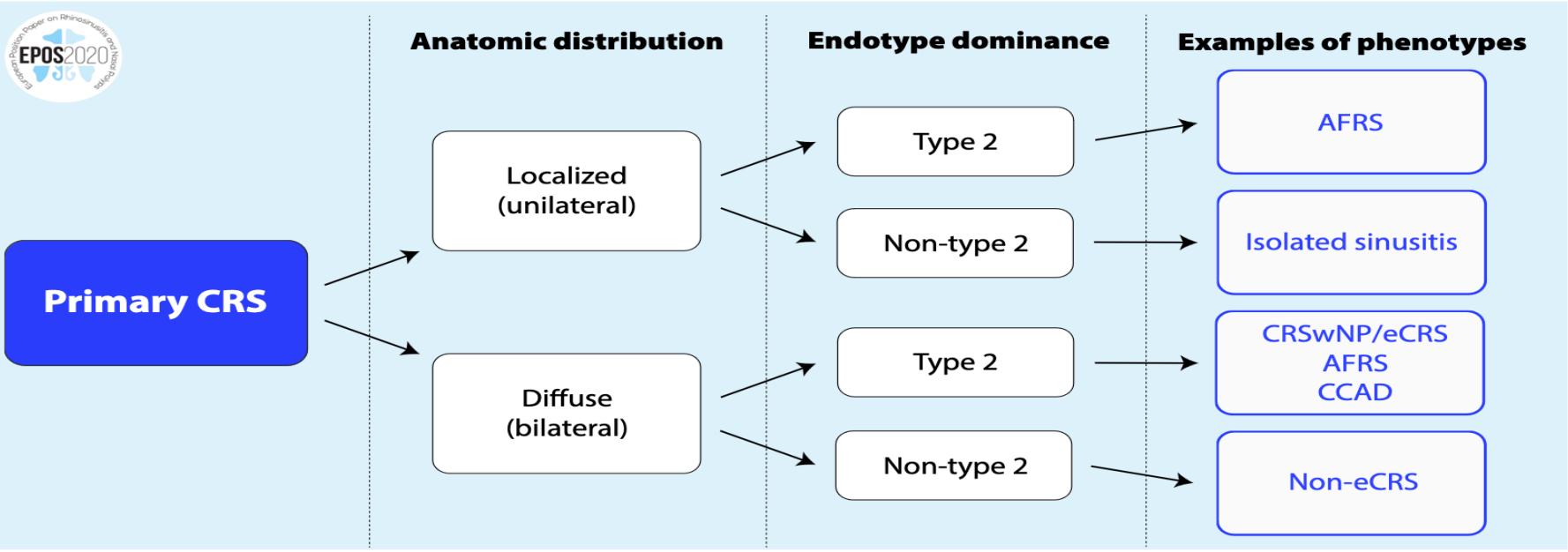
Seni paranasali (punteggio per ogni lato)
Mascellare (0,1,2)
Etmoidale anteriore (0,1,2)
Etmoidale posteriore (0,1,2)
Sfenoidale (0,1,2)
Frontale (0,1,2)
Complesso osteomeatale (0,2)*
Legenda: 0 = senza anormalità, 1 = opacamento parziale, 2 = opacamento totale; * 0 = senza ostruzione, 2 = ostruito; punteggio massimo = 12 per lato

Nei trial clinici più recenti, viene definita grave una CRSwNP che presenta un **NPS≥5** (con un punteggio minimo di 2 in ogni cavità nasale).

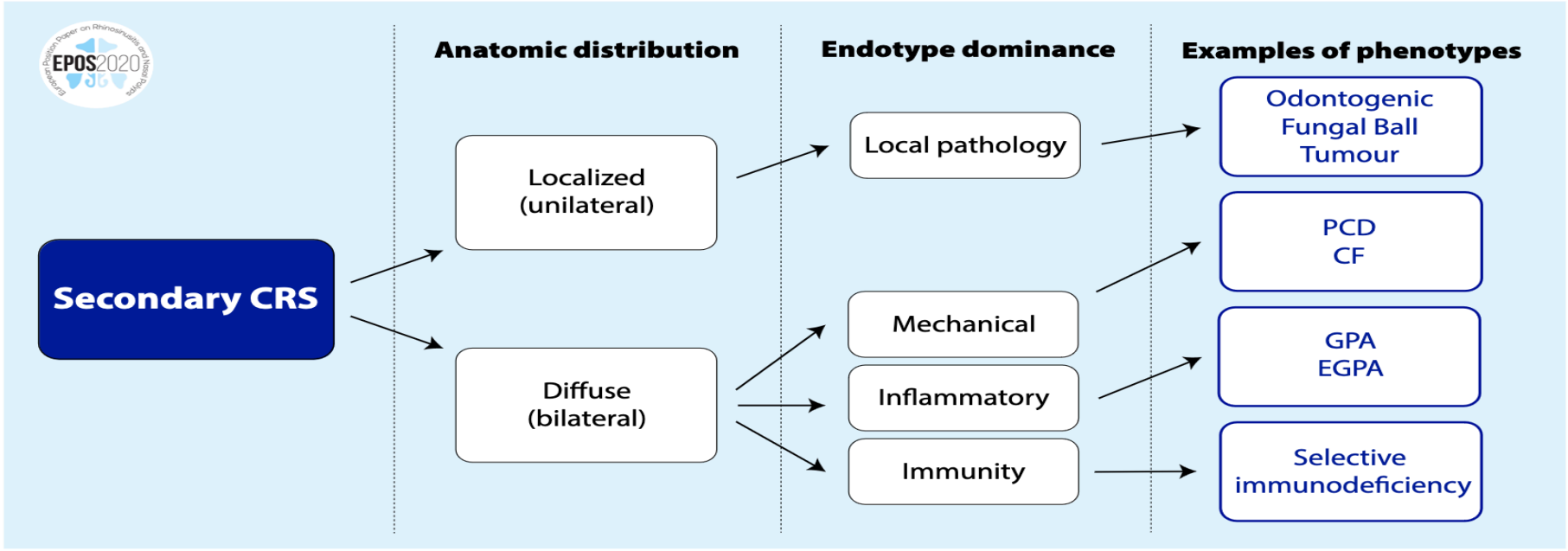
- sintomi QoL
- SNOT-22. (>50, grave)
- VAS: visual analog scale; scala grafica continua di gravità da 0 a 10.
- UPSIT/Sniffing test: valutazione dell'olfatto
- -PNIF: picco di flusso inspiratorio nasale .

CLASSIFICATION OF CHRONIC RHINOSINUSITIS





AFRS, allergic fungal rhinosinusitis; CCAD, central compartment allergic disease; CRSwNP, chronic rhinosinusitis with nasal polyps; eCRS, eosinophilic CRS.



CF, cystic fibrosis; EGPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease); GPA, granulomatosis with polyangiitis (Wegener's disease); PCD, primary ciliary dyskinesia.

EPOS 2020: Care pathways for CRS

Self-Care Pharmacy

Two **CRS** symptoms
One of which should be **nasal obstruction** and/or **discoloured discharge**
± facial pain/pressure
± reduction or loss of smell
> 12 weeks

Self-Care
- Self-education / e-Health
- Saline spray / rinses
- INCS (if OTC)
- Avoid antibiotics
- Avoid exacerbating factors

6-12 weeks: improvement?

PRESENCE OF ALARM SYMPTOMS
- Periorbital oedema/erythema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced visual acuity
- Severe headache
- Frontal swelling
- Signs of sepsis
- Signs of meningitis
- Neurological signs
- Unilateral symptoms
- Bleeding
- Crusting
- Cacosmia

IMMEDIATE REFERRAL

Refer to **Primary Care**

Primary Care

Primary care follow-up
- Saline rinses
- INCS (if not OTC)
- Educate compliance/technique
- Avoid antibiotics
- Check treatable traits and comorbidities

6-12 weeks: improvement?

Refer to **Secondary / Tertiary Care**

Secondary / Tertiary Care

Check **treatable traits** / **comorbidities**
History and full **ENT exam**
Nasal **endoscopy**

Diffuse / bilateral CRS → Follow **EPOS 2020 management scheme** on diffuse / bilateral CRS

Localized / unilateral CRS → **CT scan** (urgent if suspicion of tumour)
- **Diagnosis rejected** — Reconsider differential diagnosis
- **Diagnosis confirmed** — Surgery likely; Refer if necessary / suspected malignancy

No (apparent) CRS → **Consider CT scan** — Reconsider differential diagnosis

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Diffuse / bilateral CRS

Primary diffuse CRS

Presence of:
- Bleeding / crusting
- Severe pain
- Tissue loss
- Involvement of other organs

Secondary diffuse CRS (e.g. vasculitis / immune disorder)
- Serologic investigations
- Consider biopsy
- CT scan
- Involve appropriate specialists to treat underlying disease

Appropriate medical therapy (AMT)
- Nasal steroid (drops / spray / rinses)
- Saline rinses
- Educate technique / compliance
- Consider OCS

6-12 weeks: improvement?

ALARM SYMPTOMS
- Periorbital oedema/erythema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced visual acuity
- Severe headache
- Frontal swelling
- Signs of sepsis
- Signs of meningitis
- Neurological signs
- Unilateral symptoms
- Bleeding
- Crusting
- Cacosmia

Additional work-up:
CT-scan, SPT, lab; reconsider treatable traits, compliance

Non-type 2
- Main complaint often discharge/facial pain
- Less asthma
- Less atopy

NE: purulence
Lab: normal IgE, no eosinophilia

Type 2
- Main complaint often smell loss or blockage/congestion
- N-ERD and/or asthma
- Atopy

NE: polyps, eosinophilic mucin
Lab: elevated IgE, eosinophilia

AFRS
- Young
- Atopy
- Warm humid climate
- Asthma
- SPT: positive for fungi

Consider:
- MRI of sinuses with contrast
- Ophthalmology and neurosurgery consultation
- Preoperative OCS

AMT (± longterm antibiotics) or **FESS**

AMT (± OCS) or **FESS**

6-12 weeks: improvement?

FESS
- **Tailored (extended) surgery** to remove all debris
- **Histopathology** eosinophils, hyphae, CL crystals
- **Culture** fungus

Additional therapy
Consider:
- Xylitol rinses
- Longterm antibiotics
- Revision surgery

Additional investigations
Consider:
- Secondary diffuse CRS (e.g. vasculitis / immune disorder)

Additional therapy
Consider:
- Biologicals
- ATAD in case of N-ERD
- OCS taper
- Revision surgery

6-12 weeks: improvement?

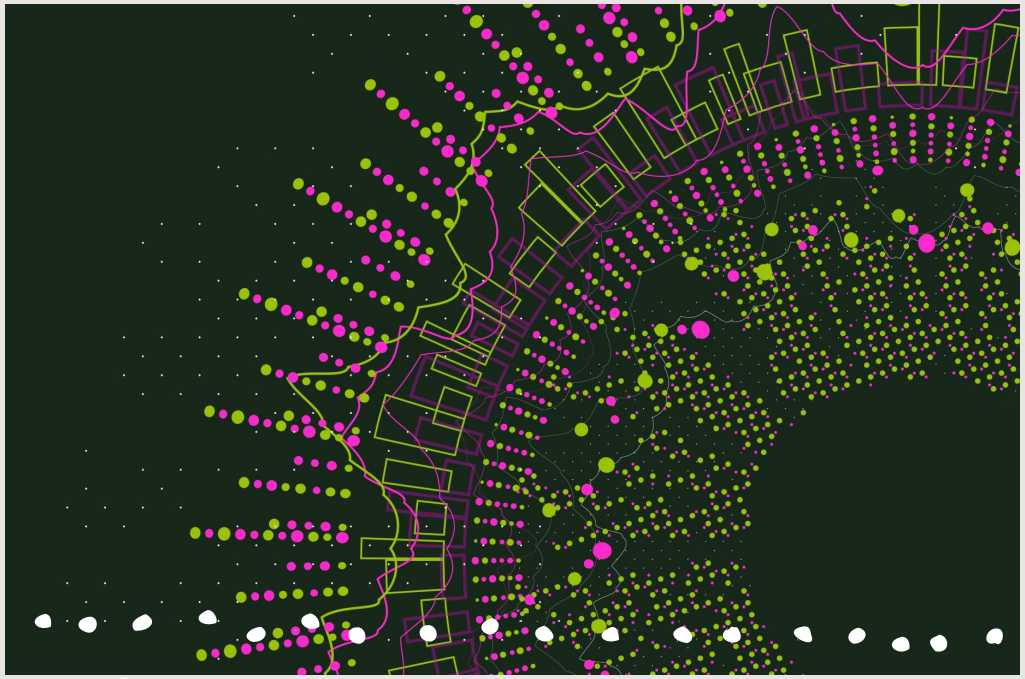
Saline rinses
INCS
OCS
Consider immunotherapy

Repeat imaging with concern for recurrence

Considerazioni e terapia

- Si pensava che l'allergia (rinite allergica) fosse causa diretta della NP , mentre gli studi più recenti hanno mostrato che la NP è presente in circa il 2-4% dei soggetti allergici, come nella popolazione generale…
- Le uniche correlazioni "forti" si osservano tra **rinite ed asma** e tra **asma grave e poliposi**, ma non tra poliposi e rinite.
- Lo standard of care è comunque la **chirurgia endoscopica**: si limita a disostruire e non è risolutiva in quanto non agisce sulle cause della malattia.
- Così come la rimozione di un tumore senza chemioterapia non previene le recidive, la chirurgia per la CRSwNP, **non impedisce la recidiva** se non si affronta l'infiammazione alla base
- Le conoscenze attuali, rivelando le caratteristiche dell'infiammazione tipo 2 che accomunano asma e NP, hanno portato alla possibile introduzione dei farmaci biologici nel trattamento "medico" della patologia,come rilevato dal recente documento **"Euforea"** .

ENDOTYPING THERAPY



AVANZAMENTI FARMACOLOGICI

E TECNOLOGICI

Terapia nella CRS

Table 7.4.1. Evidence supporting therapy of CRS in children.

Therapy	Level of evidence	GRADE recommendation
Antibiotics	1b (-)	There is no high level evidence to support the efficacy of either short or long term antibiotics for CRS in children.
Nasal corticosteroids	5	There is no evidence regarding the efficacy of intranasal steroids in the treatment of CRS in children. Nevertheless the EPOS steering group is supportive of their use in light of their anti-inflammatory effects and excellent safety record in children.
Systemic Steroids	1b (+)	Adding a taper course of systemic steroids to an antibiotic (not effective on its own) is more effective than placebo in the treatment of paediatric CRS. Judicious use of this regimen is advised considering systemic side effects.
Saline Irrigation	Ib (+)	There are a few clinical trials demonstrating the efficacy of saline irrigations in paediatric patients with CRS. The EPOS steering group is supportive of the use of saline in light of the excellent safety record in children.
Adenoidectomy	4	Adenoidectomy is effective in younger children with symptoms of CRS. The EPOS steering group supports adenoidectomy in young children refractory to appropriate medical therapy.

RSA	ANTIBIOTICO
FORME LIEVI	**Amoxicillina 50mg/Kg/die in 3 dosi per os**
FORME LIEVI con atb nei precedenti 90gg ;comunità; rischio di atb resistenza	**Amoxicillina-Ac.Clavulanico 80-90 mg/Kg/die in 3 dosi per os** Acetossietilcefuroxima 30 mg/Kg/die in 2 dosi per os Cefaclor 50 mg/Kg/die in 2 dosi per os
GRAVE COMPLICATA	**Ceftriaxone 100 mg/kg/die in dose unica per via endovenosa** Cefotaxima 100 mg/kg/die in 3 dosi per via endovenosa Amoxicillina-acido clavulanico 100 mg/kg/die, come amoxicillina, in 3 dosi per via endovenosa Ampicillina-sulbactam 100 mg/kg/die, come ampicillina, in 3 dosi per via endovenosa
GRAVI SENZA COMPLICAZIONI	**Amoxicillina-acido clavulanico 80-90 mg/kg/die per os in 3 dosi** Il passaggio alla terapia endovenosa può essere previsto quando dopo 24-48 se non miglioramento

- ✓ **S. Aureus e batteri gram- anaerobi della flora orale predominano nella CSR**
- ✓ **la prima scelta di terapia antimicrobica è generalmente empirica**
- ✓ **in caso di fallimento della terapia o deterioramento clinico, terapia mirata dopo cultura**

TRADIZIONE:

Il trattamento della CRSwNP si basa tradizionalmente su procedure mediche, inclusi corticosteroidi sistemici e locali e chirurgia endoscopica del seno (ESS)

DEFINIZIONE:

la definizione endotipica ha offerto una nuova soluzione medica mirando a..

INNOVAZIONE:

La nuova era dei farmaci biologici

Ad oggi alcuno studio randomizzato e controllato a supporto dell'efficacia degli ICS nei bambini. Tuttavia, EPOS 2020 ne supporta l'uso alla luce dei loro effetti antinfiammatori e dell'eccellente profilo di sicurezza nell'infanzia.

CORTISONICI INTRANASALI PIETRA ANGOLARE DELLA TERAPIA

Evidence supporting therapy in children

Therapy	Level of evidence	GRADE recommendation
Antibiotics	1b (-)	There is no high level evidence to support the efficacy of either short or long term antibiotics for CRS in children.
Nasal corticosteroids	5	There is no evidence regarding the efficacy of intranasal steroids in the treatment of CRS in children. Nevertheless the EPOS steering group is supportive of their use in light of their anti-inflammatory effects and excellent safety record in children.
Systemic Steroids	1b (+)	Adding a taper course of systemic steroids to an antibiotic (not effective on its own) is more effective than placebo in the treatment of paediatric CRS. Judicious use of this regimen is advised considering systemic side effects.
Saline Irrigation	Ib (+)	There are a few clinical trials demonstrating the efficacy of saline irrigations in paediatric patients with CRS. The EPOS steering group is supportive of the use of saline in light of the excellent safety record in children.
Adenoidectomy	4	Adenoidectomy is effective in younger children with symptoms of CRS. The EPOS steering group supports adenoidectomy in young children refractory to appropriate medical therapy.
FESS	4	FESS is safe and effective for the treatment of older children with CRS refractory to medical therapy or previous adenoidectomy.

CRS, chronic rhinosinusitis; FESS, functional endoscopic sinus surgery.

Tipo di Rinosinusite	Cortisonico Raccomandato	Commenti
CRSwNP (con polipi nasali)	**Mometasone furoato**	Potente con bassa sistemicità. Indicato per ridurre la crescita dei polipi e l'infiammazione eosinofilica.
	Fluticasone furoato	Buona penetrazione nei seni nasali. Efficace per ridurre polipi e sintomi.
CRSsNP (senza polipi nasali)	**Budesonide**	Usato anche nelle irrigazioni saline per migliorare la distribuzione. Indicazione per forme meno severe.
	Beclometasone	Buon profilo di sicurezza per uso a lungo termine, meno potente di altri corticosteroidi ma adatto a trattamenti estesi.
CRS eosinofilica grave	**Mometasone furoato**	Cortisonico di prima linea per casi gravi con eosinofili elevati. Riduce infiammazione Th2 e crescita dei polipi.
CRS con asma	**Fluticasone furoato**	Indicato per ridurre sia i sintomi nasali che asmatici. Buona penetrazione nelle cavità nasali.
CRS resistente a cortisonici topici	**Spray con dosaggio elevato** (es. Fluticasone 800 µg)	Usato in casi di CRS refrattario, con aumento della dose rispetto al trattamento standard per ridurre i polipi.

Nasal corticosteroids	1a	There is high-quality evidence that long term use of nasal corticosteroids is effective and safe for treating patients with CRS. They have impact on nasal symptoms and quality of life improvement, although the effect on SNOT-22 is smaller than the minimal clinically important difference. The effect size on symptomatology is larger in CRSwNP (SMD -0.93, 95% CI -1.43 to -0.44) than in CRSsNP (SMD -0.30, 95% CI -0.46). The meta-analysis did not show differences between different kinds of nasal corticosteroids. Although in meta-analysis higher dosages and some different delivery methods seem to have a larger effect size on symptomatology, direct comparisons are mostly missing. For CRSwNP, nasal corticosteroids reduce nasal polyp size. When administered after endoscopic sinus surgery, nasal corticosteroids prevent polyp recurrence. Nasal corticosteroids are well tolerated. Most adverse events reported are mild to moderate in severity. Nasal corticosteroids do not affect intraocular pressure or lens opacity. The EPOS2020 steering group advises to use nasal corticosteroids in patients with CRS. Based on the low to very low quality of the evidence for higher dosages or different delivery methods and the paucity of direct comparisons the steering committee cannot advise in favour of higher dosages or certain delivery methods.

- **Efficacia dei cortisonici intranasali**: sono efficaci e sicuri

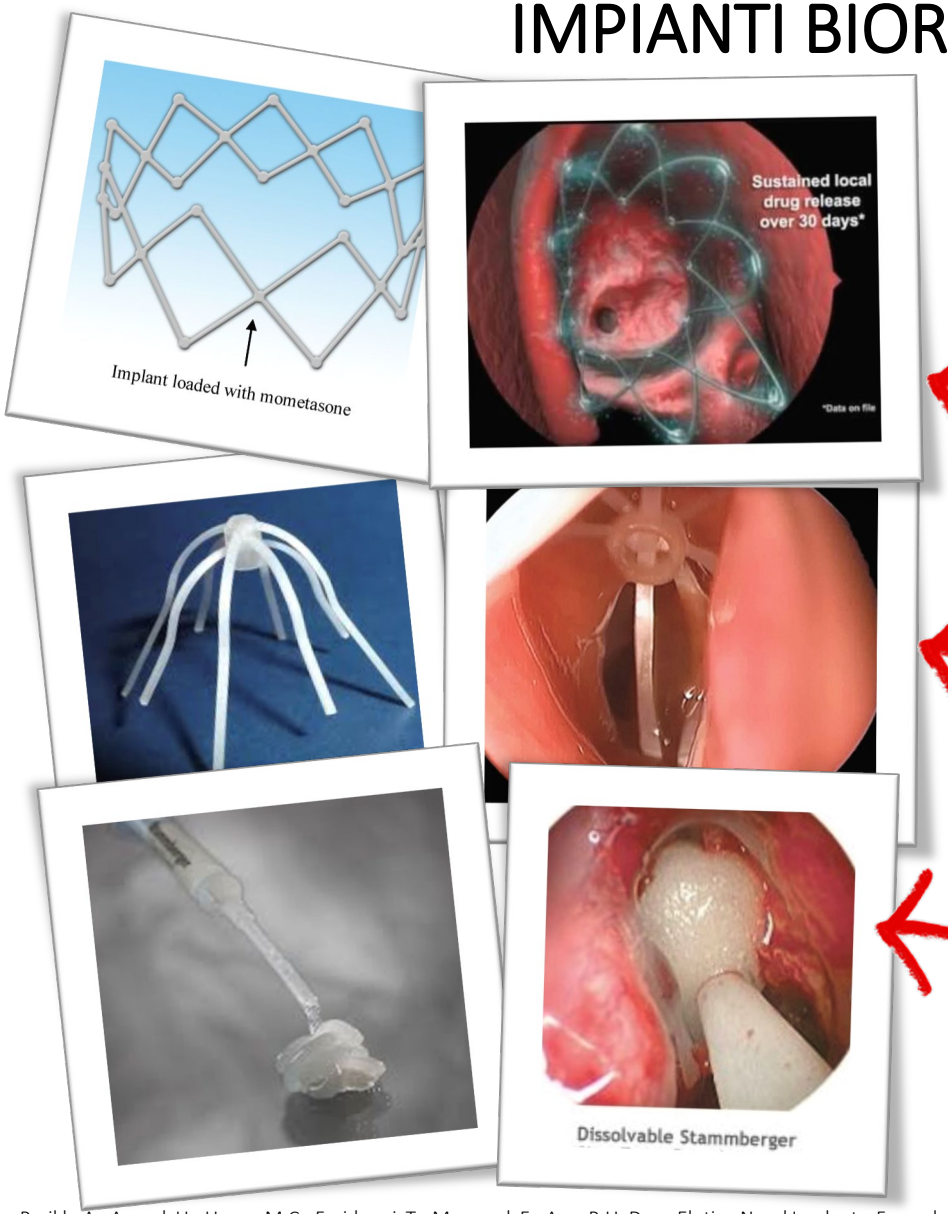
- **Non ci sono differenze tra i vari tipi di cortisonici (e forze nemmeno fra i dosaggi)**: Le meta-analisi non hanno mostrato differenze significative tra i diversi tipi di corticosteroidi intranasali, anche se alcuni dosaggi elevati sembrano avere un effetto maggiore sui sintomi. Tuttavia, non ci sono abbastanza confronti diretti per trarre conclusioni definitive.

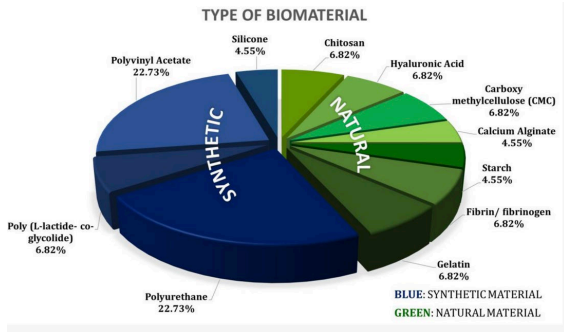
QUALE INCS SCEGLIERE

Tipo di Formulazione	Esempi di Farmaci	Caratteristiche	Vantaggi	Svantaggi
Acquosa	Fluticasone furoato, Mometasone	Più delicata per la mucosa.	- Maggiore tollerabilità. - Minore irritazione.	- Possibile minor durata d'azione rispetto ad altre formulazioni.
Alcolica	Beclometasone	Favorisce un rapido assorbimento.	- Rapido assorbimento. - Effetto astringente, utile per rinorrea.	- Possibile irritazione o bruciore alla mucosa. - Secchezza nasale.
Sospensione	Budesonide	Maggiore adesione.	- Miglior adesione alla mucosa. - Maggiore durata d'azione.	- Richiede agitazione prima dell'uso. - Distribuzione meno uniforme.
Gel	Formulazioni sperimentali	Rilascio graduale	- Lunga durata di applicazione. - Minore irritazione.	- Possibile sensazione di disagio o appiccicosità. - Rilascio meno rapido.
Propellente a gas	Beclometasone con propellente	Distribuzione uniforme	- Penetrazione più profonda. - Facile applicazione.	- Possibile sensazione di freddo o disagio nel naso. - Potenziale irritazione.
Irrigazioni saline con corticosteroide	Budesonide	Miscelato in soluzione salina per irrigazioni	- Distribuzione su tutta la cavità nasale. - Utile in CRS grave.	- Richiede maggior impegno e tempo rispetto a uno spray.

INNOVAZIONE BIOTECNOLOGICA

IMPIANTI BIORIASSORBIBILI A RILASCIO DI STEROIDI

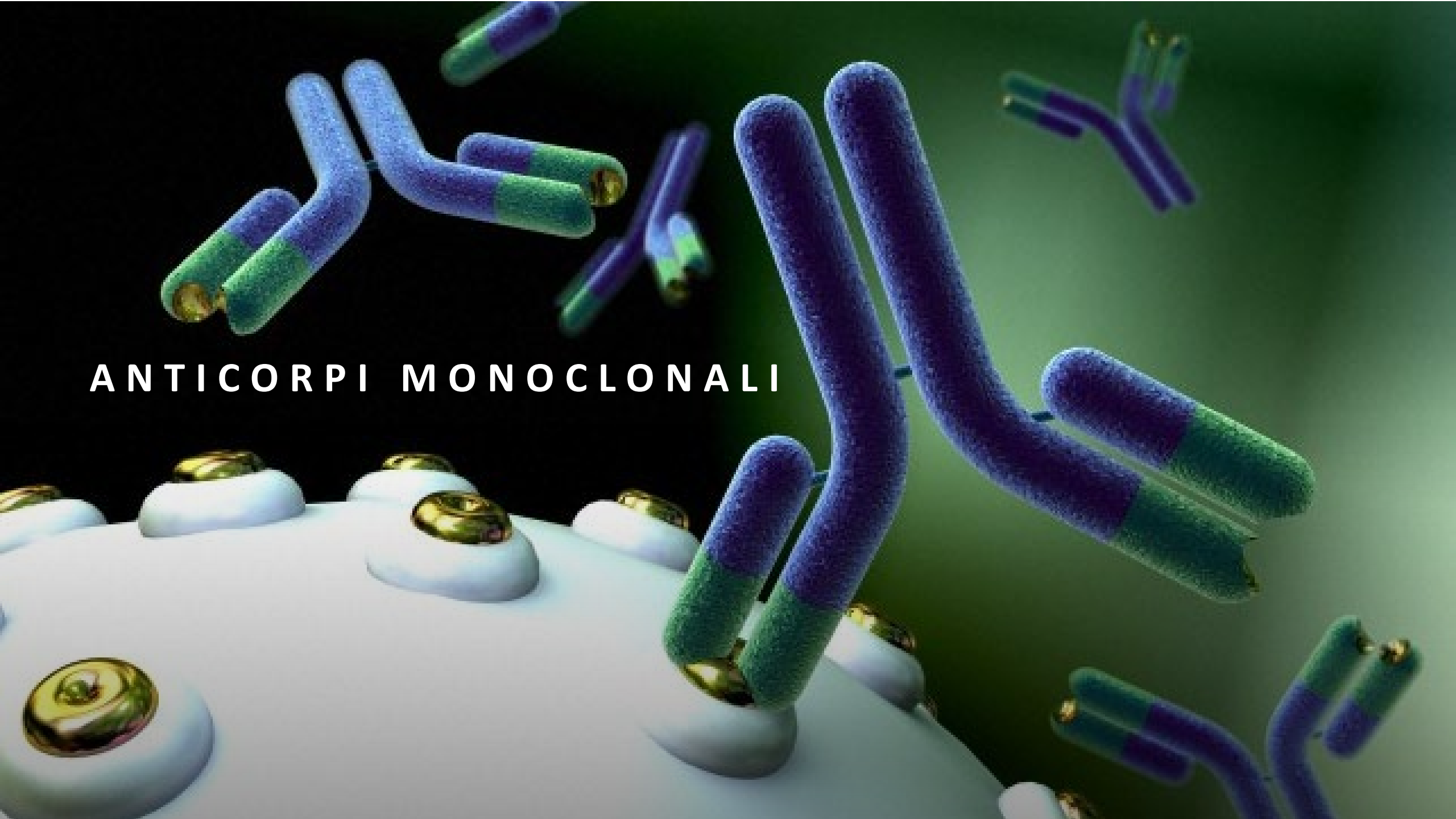




FDA Approved Nasal Stents/Implants	Advantages
Propel™ sinus implant	Reduces inflammation associated with CRS and promotes wound healing; Implant is made of PLGA (a biodegradable polymer) and is the first and the only FDA approved biodegradable implant for the treatment of CRS; Does not require a second surgical procedure to remove the implant; Releases the drug slowly and continuously for over a month
Relieva stratus™ MicroFlow spacer	Potential to reduce chronic inflammation. Minimal invasive approach for targeted local delivery of therapeutic agents slowly and continuously to the site of action
Sinu-Foam™ spacer	Promotes wound healing and reduces chronic inflammation of sinus and nasal mucosa

Parikh, A.; Anand, U.; Ugwu, M.C.; Feridooni, T.; Massoud, E.; Agu, R.U. Drug-Eluting Nasal Implants: Formulation, Characterization, Clinical Applications and Challenges. *Pharmaceutics* **2014**, *6*, 249-267.

Shen, J., Welch, K., & Kern, R. **(2018)**. *Mometasone furoate sinus implant - a new targeted approach to treating recurrent nasal polyp disease. Expert Review of Clinical Pharmacology.* Razali, R.A.; Vijakumaran, U.; Fauzi, M.B.; Lokanathan, Y. Maximizing Postoperative Recovery: The Role of Functional Biomaterials as Nasal Packs—A Comprehensive Systematic Review without Meta-Analysis (SWiM). *Pharmaceutics* **2023**, *15*, 1534


ANTICORPI MONOCLONALI

Indications for biological treatment in CRSwNP

Presence of bilateral polyps in a patient who had ESS*

THREE criteria are required

Criteria	Cut-off points
• Evidence of type 2 inflammation	• Tissue eos ≥10/hpf, OR blood eos ≥250, OR total IgE ≥100
• Need for systemic corticosteroids or contraindication to systemic steroids	• ≥ 2 courses per yr, OR long term (>3 months) low dose steroids
• Significantly impaired quality of life	• SNOT-22 ≥ 40
• Significant loss of smell	• Anosmic on smell test (score depending on test)
• Diagnosis of comorbid asthma	• Asthma needing regular inhaled corticosteroids

*exceptional circumstances excluded (e.g., not fit for surgery)

CRS, chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery; hpf: high power field (x400); SNOT-22, sino-nasal outcome test-22.

Defining response to biological treatment in CRSwNP

Evaluation of 5 criteria

- Reduced nasal polyp size
- Reduced need for systemic corticosteroids
- Improved quality of life
- Improved sense of smell
- Reduced impact of co-morbidities

Excellent response
5 criteria

Moderate response
3-4 criteria

Poor response
1-2 criteria

No response
0 criteria

↓

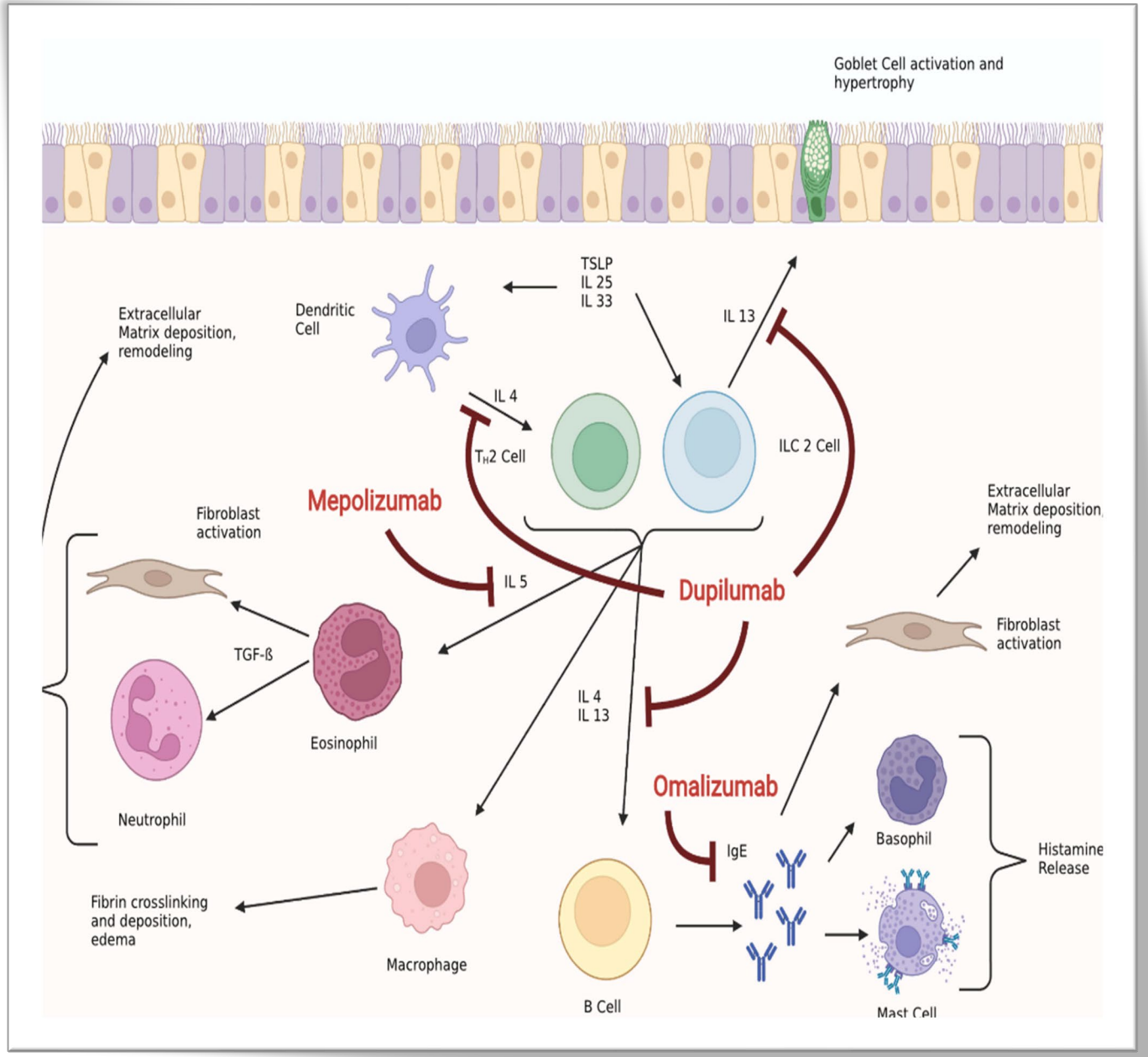
Evaluate treatment response **after 16 weeks**

→ **Discontinue treatment** if no response in any of the criteria

↓

Evaluate treatment response **after 1 year**

→ **Discontinue treatment** if no response in any of the criteria



T.Merril et al. Managing Chronic Rhinosinusitis with Nasal Polyps in the Elderly: Challenges and Solutions. Clinical Interventions in Aging **2022**:17
Ruggero et al. Pharmacological, Technological, and Digital Innovative Aspects in Rhinology Front. Allergy, 15 December 2021

Pathways	mAbs	Target	Approved indications in EU by ema	Approved indications in us by FDA	studies phase in NP, CRS, or CRSwNP, CRSsNP, AR
IgE	Omalizumab	IgE	- CRSwNP - CIU - Allergic asthma	- Nasal polyps - CIU - Allergic asthma	Phase 3 (AR)
	Ligelizumab	IgE	-	-	No trials yet
	Quilizumab	IgE	-	-	Phase 1 (AR)
IL-5	Mepolizumab	IL-5	- Eosinophilic asthma	- Eosinophilic asthma - HES - EGPA	Phase 3 (NP)
	Reslizumab	IL-5	- Eosinophilic asthma	- Eosinophilic asthma	Phase 3 (CRS)
	Benralizumab	IL-5Rα	- Eosinophilic asthma	- Eosinophilic asthma	Phase 3 (NP) Phase 3 (CRSwNP)
IL-4/IL-13	Dupilumab	IL-4Rα	- Atopic dermatitis - Asthma - CRSwNP	- Atopic dermatitis - Asthma - CRSwNP	Phase 3 (CRSnNP) Phase 4 (CRSwNP)
	Tralokinumab	IL-13	- Atopic dermatitis	- Atopic dermatitis	No trials yet
	Lebrikizumab	IL-13	-	-	No trials yet
IL-17	Brodalumab	IL-17RA	- Psoriasis	- Psoriasis	No trials yet
IL-33	Etokimab	IL-33	-	-	Phase 2 (CRSwNP)
TSLP	Tezepelumab	TSLP	-	-	Phase 3 (CRSwNP)

CIU, chronic idiopathic urticarial; AR, Allergic Rhinitis; NP, nasal polyps; TSLP, thymic stromal lymphopoietin; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps, EU, Europe; US, United States; EMA, European Medicines Agency; FDA, Food and Drugs Administration.

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Biologics for chronic rhinosinusitis

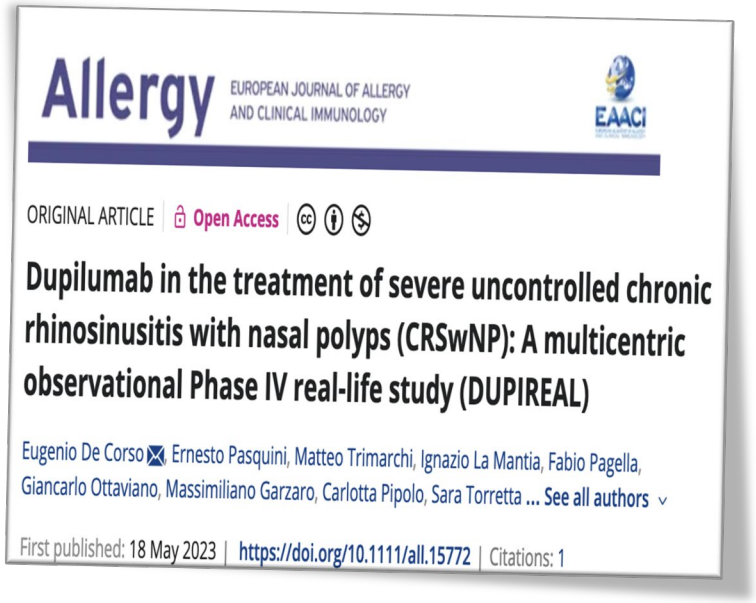
Lee-Yee Chong, Patorn Piromchai, Steve Sharp, Kornkiat Snidvongs, Katie E Webster, Carl Philpott, Claire Hopkins, Martin J Burton Authors' declarations of interest

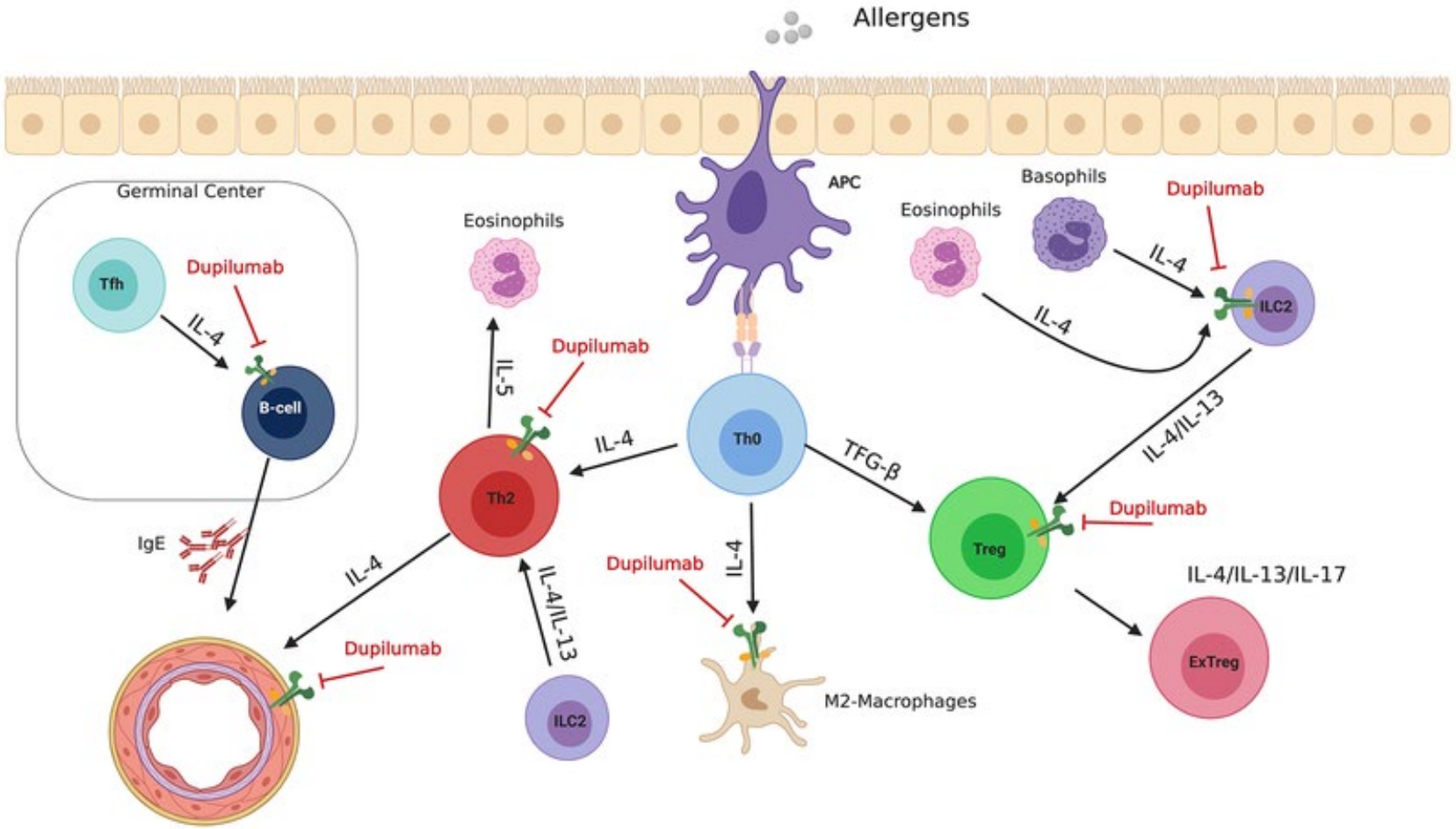
Version published: 12 March 2021 Version history

TABLE 2 | Main results of a recent Cochrane Review on the clinical management of patients with NP and CR with biologics.

mAb compared to placebo	Disease-specific HRQL	Disease severity	Serious adverse events
Dupilumab (anti IL-4)	Improve	Results in a reduction	May result in a reduction in number
Mepolizumab (anti IL-5)	May improve	Very uncertain difference	Very uncertain difference
Omalizumab (antiIgE)	Probably improve	No evidence	Very uncertain difference

ANTI-IL4/IL13: DUPILUMAB

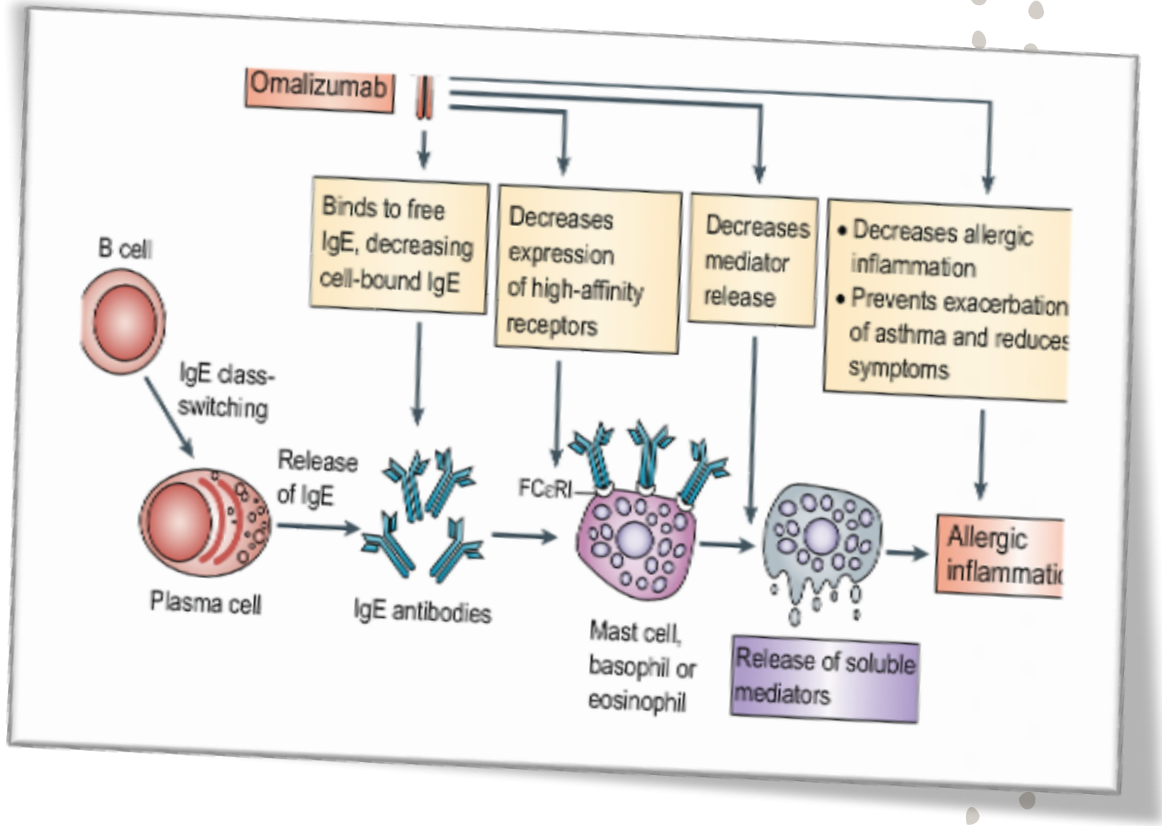




- Anti-IL4/13
- Blocca la risposta Th2
- Modula l'attivazione delle ILC2 (cellule innate linfoidi di tipo 2)
- Approvato per il trattamento della CRSwNP solo negli adulti che non hanno un adeguato controllo della malattia (FDA) e se falliscono corticosteroidi sistemici e/o chirurgia (EMA)

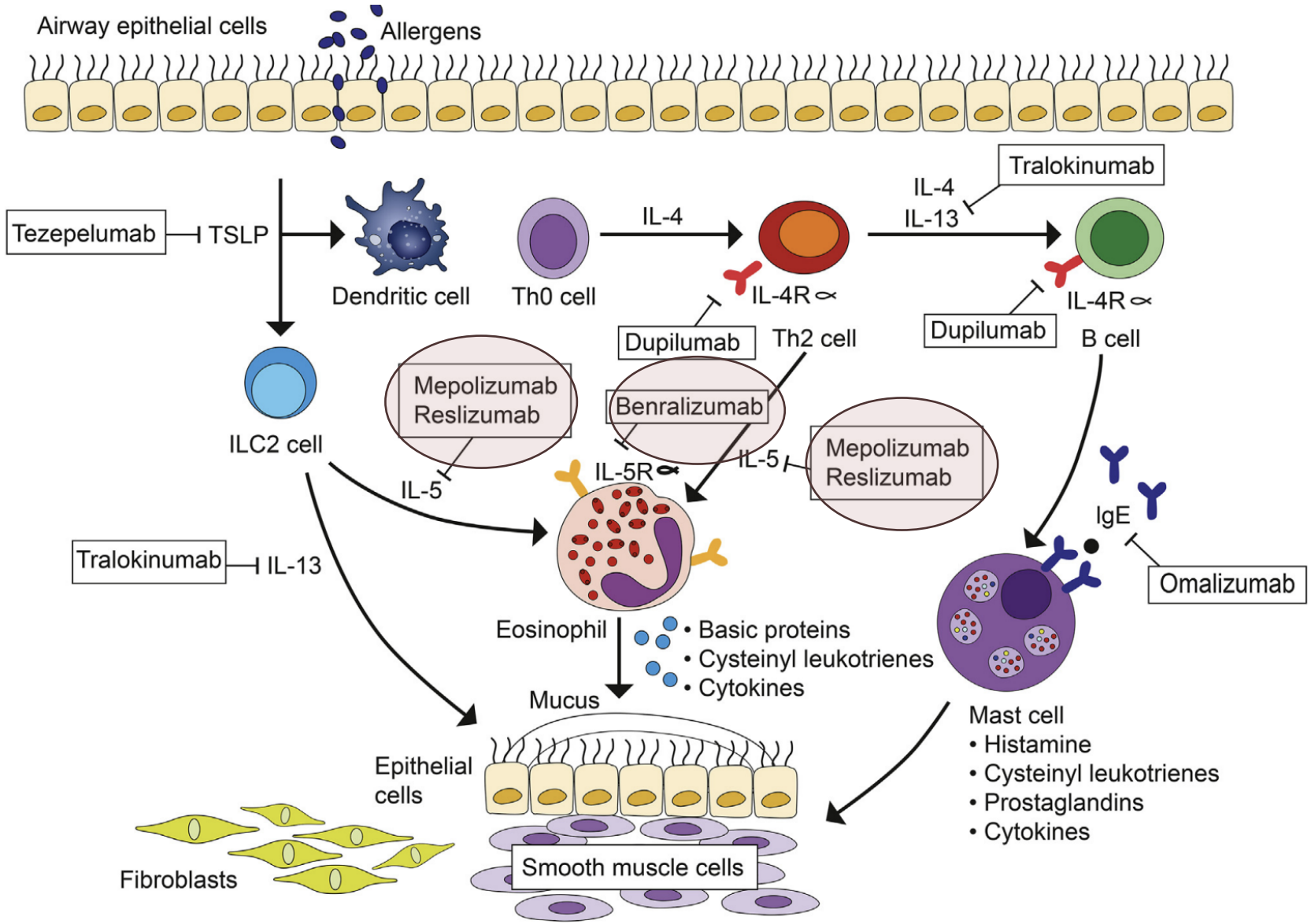
ANTI-IGE: OMALIZUMAB

- ↓ sIgE, eosinofili, basofili, mastociti e linfociti B (anergia linfociti B-IgE$^{+)}$
- In comorbilità con asma ↓ il punteggio NP e la gravità indipendentemente dalla presenza di allergia
- Studi randomizzati di Fase III, POLYP1 e POLYP2, indicano un miglioramento dopo 4 settimane di utilizzo con persistenza a 24 settimane



Indicato come terapia aggiuntiva per il trattamento degli adulti (età ≥ 18 anni) con CRSwNP grave per i quali solo la terapia corticosteroidea intranasale non fornisce un adeguato controllo.

ANTI-IL5: MEPOLIZUMAB, RESLIZUMAB E BENRALIZUMAB

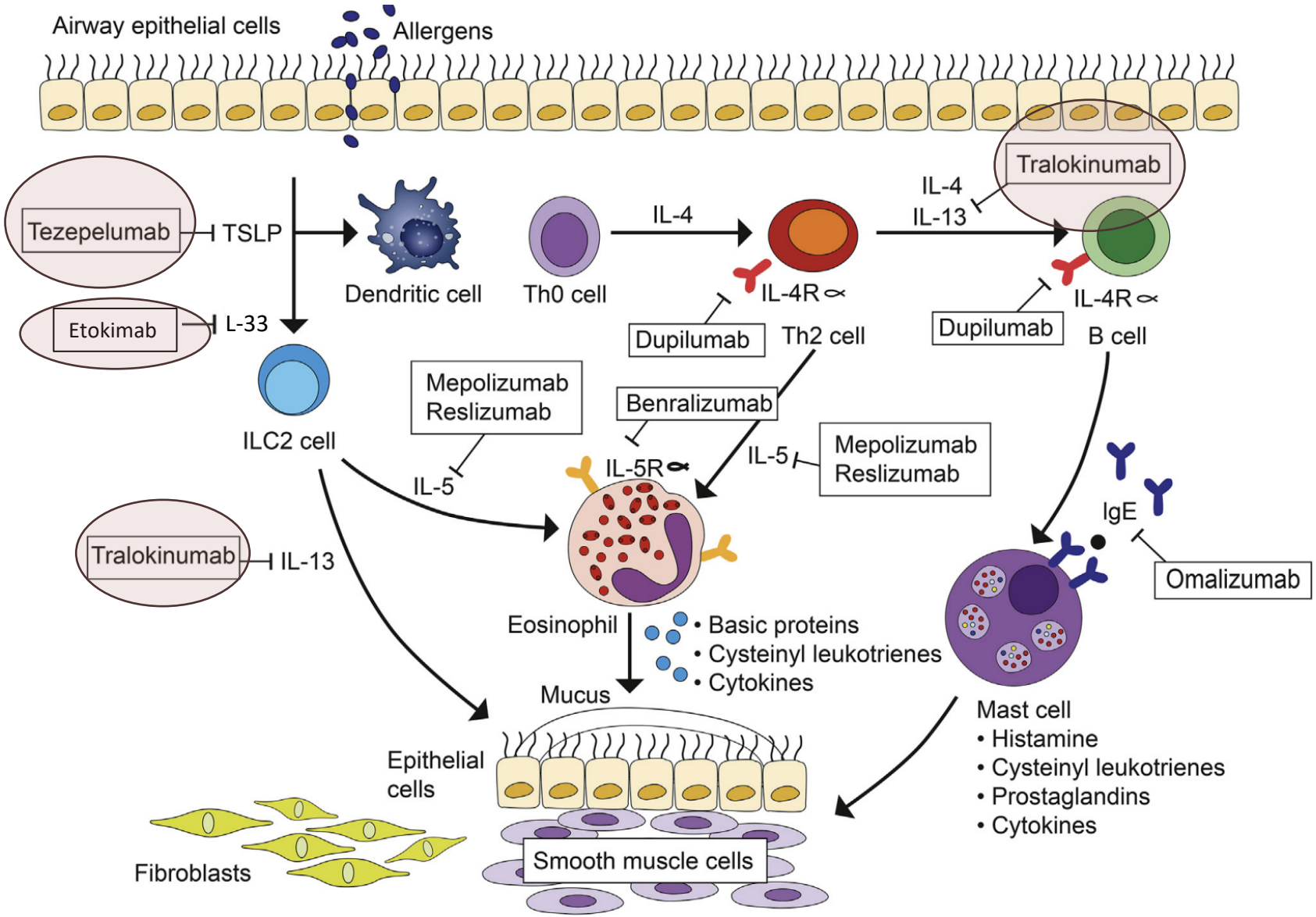


Farmaco	Meccanismo d'azione
Mepolizumab	Blocca IL-5
Reslizumab	Blocca IL-5
Benralizumab	Blocca IL-5Rα (induce apoptosi)

"antibody-dependent, cell-mediated cytotoxicity"

Apotosi eosinofili

ANTI-IL33: TEZEPELUMAB, ANTI IL-13 TRALOKINUMAB E ALTRI



Farmaco	Meccanismo d'azione
Tezepelumab	blocca il TSLP
Etokimab	Blocca IL33
Tralokinumab	Blocca IL13
Zweimab/ Doppelmab	Blocca IL13/33

…E ALTRI

Meccanismo di azione :
CRTH2 è un recettore per la **prostaglandina D2 (PGD2)** che promuove la chemiotassi e l'attivazione delle Th2, eosinofili e basofili.
Il blocco di questo recettore diminuisce contestualmente IL-4, IL-5 e IL-13.

1. **Fevipiprant**
2. **Timapiprant**
3. **Setipiprant**

Applicazione clinica:
Sono promettementi specialmente per **asma** e **CRSwNP: particolarmente nei fenotipi eosinofilici.**

…E ALTRI

Anti-CXCR2

anti-IL17A

Inibitore recettore P2Y12 (plasugrel)

Inibitore della 5-lipossegenasi (Zileuton)

Anti SIGLEC-8 (sialic acid-binding Ig-like lectin 8)

Anti- Leucotrieni (Montelukast, ZafirLukast)

Inibitore recettore T prostanoide (Ifetroban)

mySinusitisCoach

QUALE BIOLOGICO SCEGLIERE?

TABLE 1 The three biologic agents assessed in the 20 studies of randomized controlled trials (RCTs) and case series included in the present analysis.

Biologic agent	Number of RCTs (out of total included) level of evidence	Primary endpoints	Secondary endpoints	Measures used	Outcomes in brief
Omalizumab	4/20 Level of evidence: II	Change from baseline in NPS Nasal congestion score (NCS) Imaging scores Change from baseline in sense of smell and nasal discharge Need for surgery (NFS) Need for systemic corticosteroids (ROCS)	Blood eosinophil count Serum total IgE Thymus and activation regulated chemokine Plasma eotaxin-3 Eosinophilic cationic protein Total IgE in nasal secretions	NPS NCS SNOT-22 VAS-symptom scale UPSIT LoS LMK score PNIF FEV FVC PEFR AQLQ TNSS	Omalizumab demonstrated significant improvements in both clinical and patient-reported outcomes. Omalizumab also appeared to be more effective than placebo even in patients with high eosinophil levels or those previously operated for CRSwNP
Mepolizumab	3/20 Level of evidence: II				Mepolizumab significantly reduced NFS and provided greater improvement than placebo in terms of symptoms severity, regardless of the presence of aspirin-exacerbated respiratory disease or comorbid asthma.
Dupilumab	13/20 Level of evidence: II				Dupilumab provided significant improvements across all outcomes, including NPS, NCS, and LMK score. Dupilumab also appeared to be significantly more effective than placebo in reducing both NFS and need of ROCS Dupilumab efficacy appeared to be independent of baseline eosinophils/IgE values or comorbidities

TABLE 2 The three biologic agents assessed in the 17 systematic reviews—meta-analyses and indirect treatment comparison studies (ITCs) included in the present study.

Biologic agent	Number of systematic reviews/meta-analyses/ICTs (out of total included)/level of evidence	Primary endpoints assessed	Secondary endpoints assessed	Measures involved	Outcomes in brief
Omalizumab	17/17 Level of evidence: I	Clinical and imaging scores Need for systemic corticosteroids (ROCS) Need for Surgery (NFS) Quality of life reports Adverse events	Blood eosinophil count Th-2 cell-associated biomarkers SF-36 RSOM-31	NPS NCS SNOT-22 VAS-symptom scale UPSIT LoS LMK score PNIF FEV FVC PEFR AQLQ TNSS	The vast majority of the systematic reviews and meta-analyses, included in this study demonstrated that omalizumab, dupilumab, and mepolizumab appeared to be effective and significantly better in reducing the severity of symptoms (NPS, NCS) and the need for rescue medication and/or surgery (ROCS, NFS) compared with placebo. All three agents improved the sense of smell compared with placebo, although to a different degree in terms of responder rate and degree of improvement. Only one systematic review[45] was focused on comparative assessment of the three biologics, showing that dupilumab appeared to be the most beneficial agent, in terms of improvement of both primary and secondary outcomes evaluated.
Mepolizumab	13/17 Level of evidence: I				
Dupilumab	13/17 Level of evidence: I				

Consensus Multidisciplinare ARIA-ITALIA: poliposi nasale e farmaci biologici

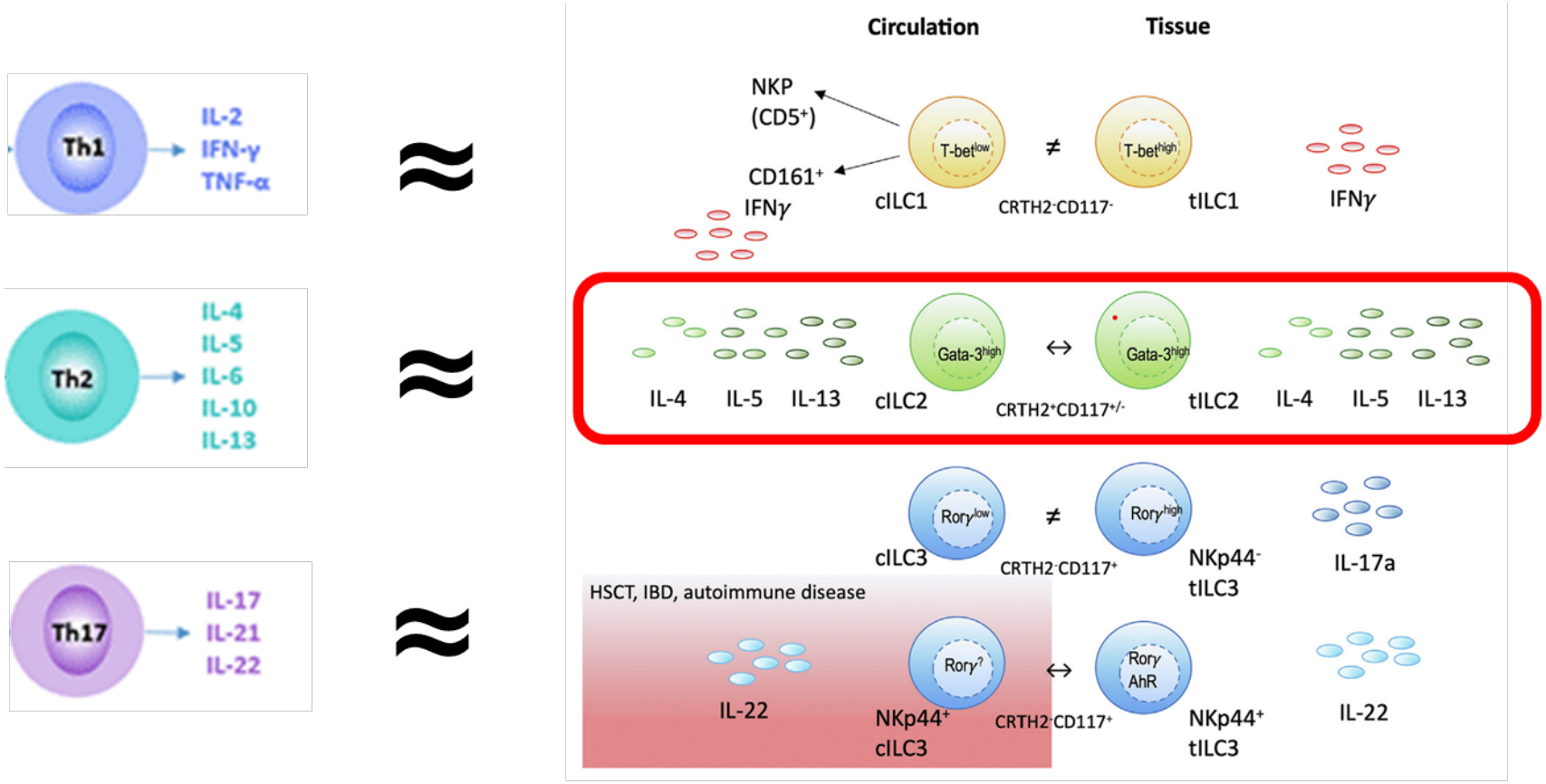
Carlo Lombardi[1] e Giovanni Passalacqua[2] per ARIA-ITALIA e Società Scientifiche aderenti*

Riccardo Asero[3], Diego Bagnasco[2], Francesco Blasi[4], Matteo Bonini[5], Mario Bussi[6], Rikki F. Canevari[7], Giorgio Walter Canonica[8], Paolo Castelnuovo[9], Lorenzo Cecchi[10], Lorenzo Cosmi[11], Matteo Gelardi[12], Enrico Heffler[8], Luciana Indinnimeo[13], Massimo Landi[14], Amelia Licari[15], Francesco Liotta[11], Alberto Macchi[16], Luca Malvezzi[17], Gianluigi Marseglia[15], Claudio Micheletto[18], Antonino Musarra[19], Diego Peroni[20], Giorgio Piacentini[21], Venerino Poletti[22], Luca Richeldi, [23], Angela Santoni[24], Michele Schiappoli[25], Gianenrico Senna[25], Adriano Vaghi[26], Alberto Villani[27]

Nome e cognome della terapia biologica

Nome: anti-IL4, anti-IL5, anti-IL13, anti-IL33, anti-TSLP ecc…

Cognome: cellule innate linfoidi (ILC)



Nome e cognome della terapia biologica

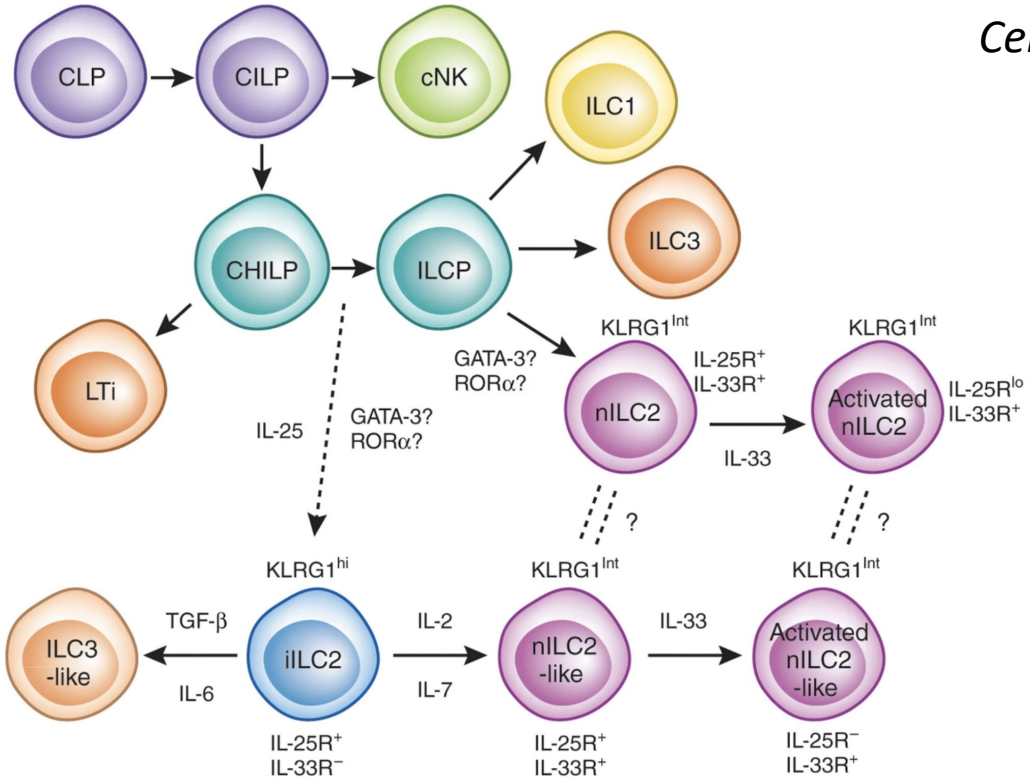
Nome: anti-IL4, anti-IL5, anti-IL13, anti-IL33, anti-TSLP ecc…

Cognome: cellule innate linfoidi (ILC**)**

Le **ILC2** sono divise in:

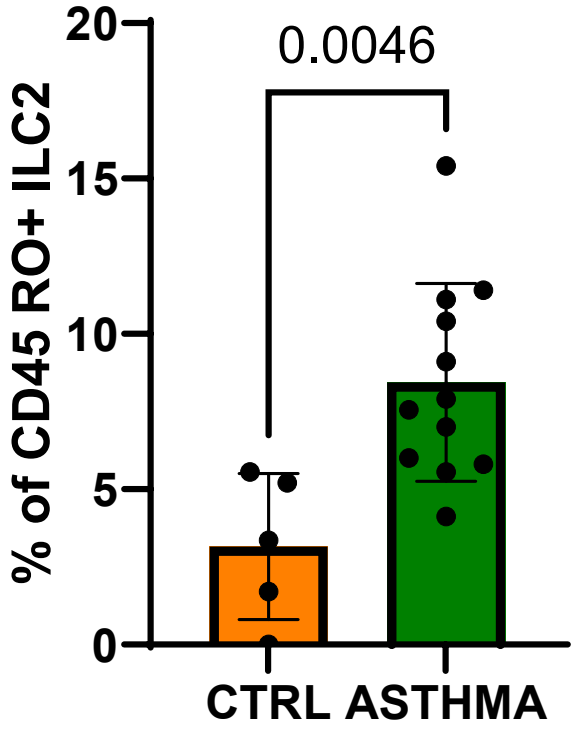
- ILC2 **naturali** (**nILC2**)
  tessuti barriera e responsive principalmente a IL-33/TSLP.

- ILC2 **infiammatorie** (**iILC2**)
  raggiungono i siti stimolate da infezione da **elminti** o **stimolazione citochinica (IL-25)**

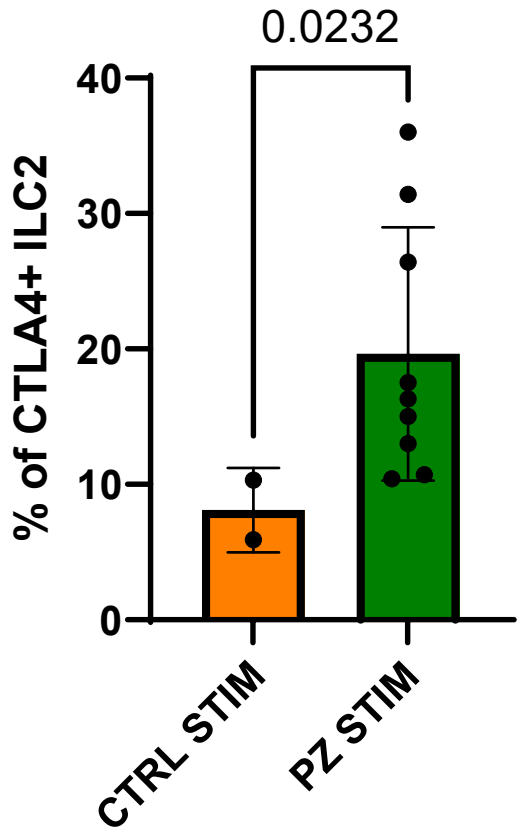


Cellule rare…
Cellule plastiche…

Espressione CTLA-4 nelle ILC2 di pazienti asmatici



Il numero di iILC2 (CD45RO^{+}) è maggiore nei pazienti asmatici rispetto ai controlli



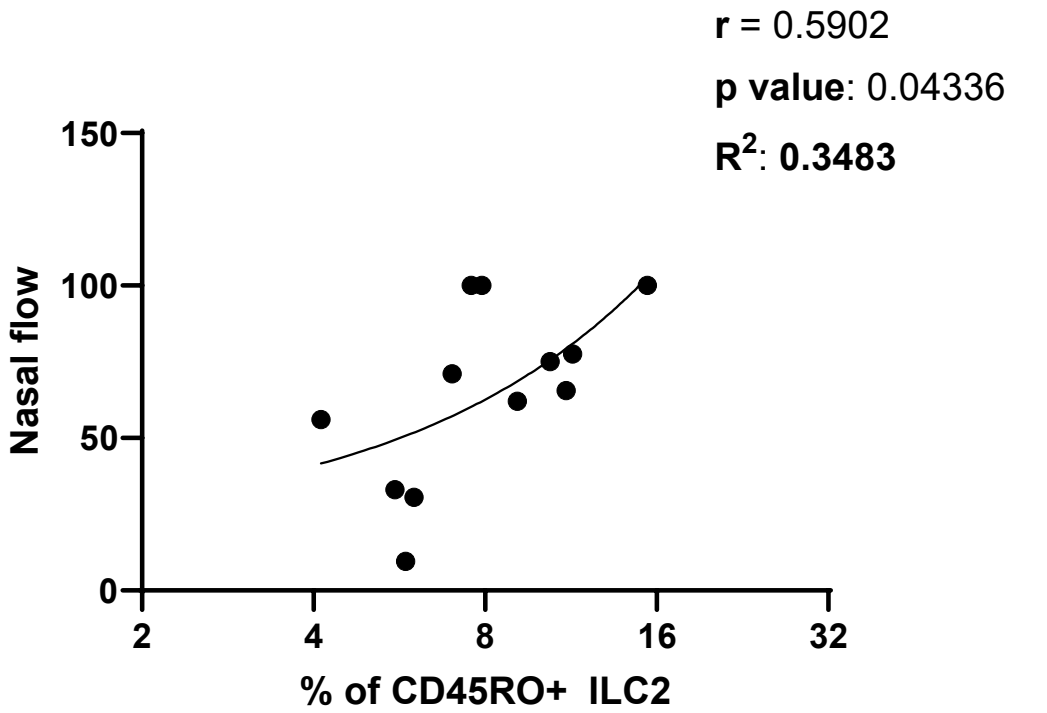
Dopo stimolazione (PMA e ionomicina) CTLA4^{+} è maggiormente espresso rispetto ai controlli

Cellule autoregolanti?

nILC2: CD45RA+, CD19-, CD3-, CD14-, CD56-, GATA3+

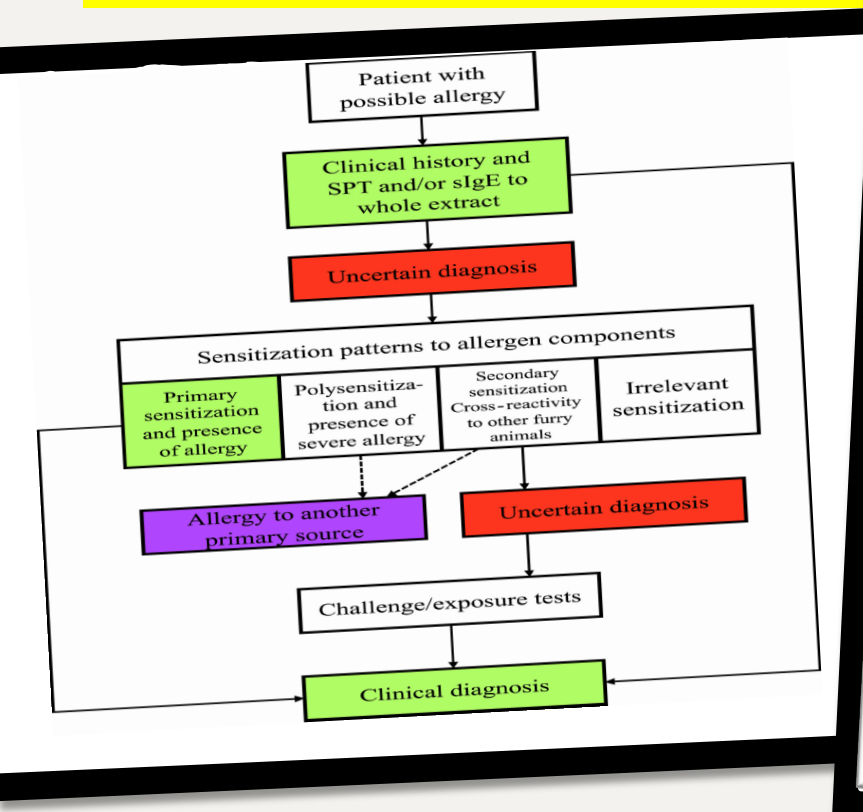
iILC2: CD45RO+, CD19-, CD3-, CD14-, CD56-, GATA3+

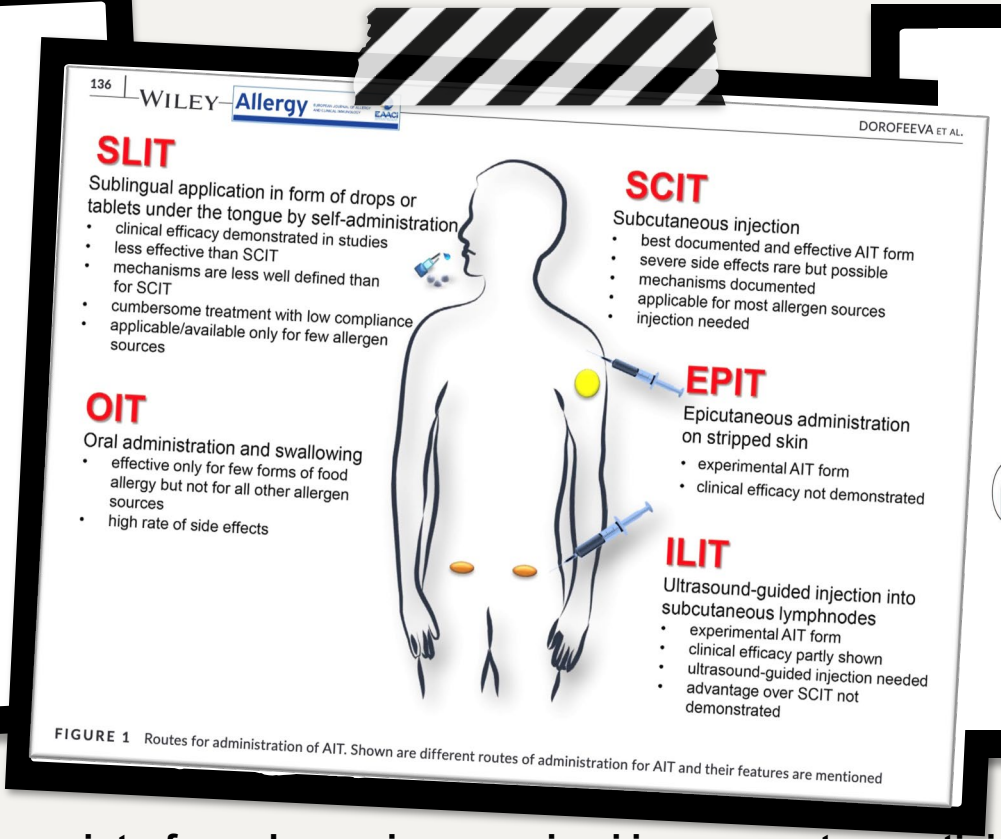
Maggiore espressione CTLA-4, maggior funzionalità respiratoria?

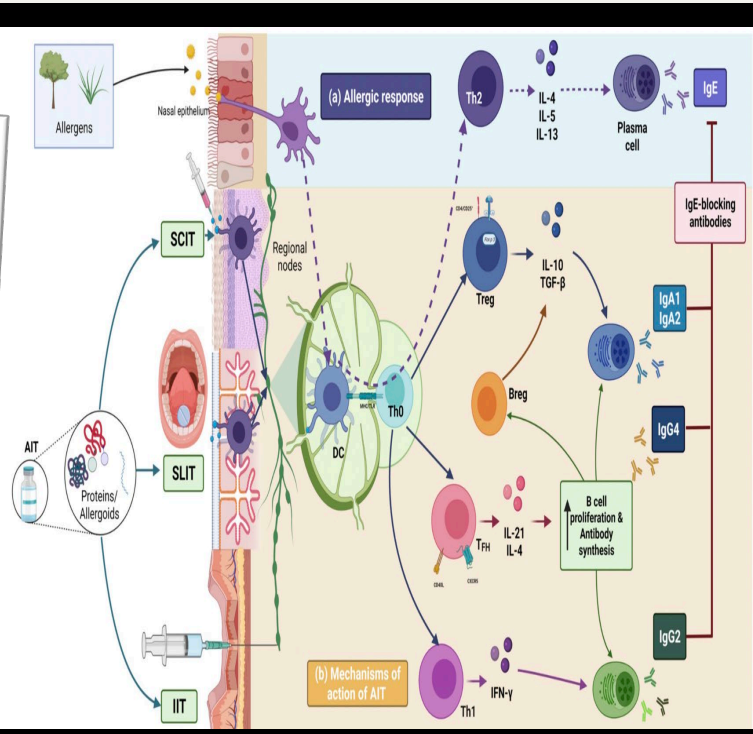


Correlazione positiva fra il valore delle ILC2 CD45RO+ e il flusso medio alla rinomanometria pre-decongestione.

COMPONENT RESOVED DIAGNOSIS E IMMUNOTERAPIA SPECIFICA







Induce la tolleranza nei confronti dell'allergene interferendo con i meccanismi immunopatogenetici alla base delle malattie allergiche, con miglioramento a lungo termine dei sintomi modulando il corso naturale della malattia.

- ❑ **riduzione delle IgE specifiche per l'allergene;**
- ❑ **induzione di anticorpi IgG allergene specifici che bloccano l'attivazione allergene-indotta delle cellule immunocompetenti;**
- ❑ **riduzione della sintesi di citochine Th2 che favoriscono lo sviluppo della reazione allergica e l'attivazione delle cellule coinvolte**
- ❑ **L'ITS riduce l'infiammazione allergene-specifica dell'organo bersaglio.**

L'UNICO STRUMENTO TERAPEUTICO " DISEASE MODIFYING

Pavón-Romero, G.F.; Parra-Vargas, M.I.; Ramírez-Jiménez, F.; Melgoza-Ruiz, E.; Serrano-Pérez, N.H.; Teran, L.M. Allergen Immunotherapy: Current and Future Trends. *Cells* **2022**, *11*, 212.

TAKE HOME MESSAGES

1. La CRS è rara in pediatria, ma le sue complicazioni richiedono una terapia mirata

2. Oltre suddivisione in CRSsNP/CRSwNP è opportuno **riconoscere multipli endotipi**

3. Gli **ab monoclonali agiscono con successo**, ma non agisce sull'eziologia in termini permanenti e non esiste un consensus per l'utilizzo in pediatria. Non sono candidati i pazienti con patologie specifiche (FC).

4. Su base allergica l'ITS è l'unica terapia capace di modificare la patologia

Futuro

1. Studiare il vero ruolo delle **cellule innate linfoidi**, possibili nuovi target terapeutici e predittori di malattia

2. Considerare l'immunomodulazione già in atto da parte delle cellule infiammatorie e adiuvarle verso un evoluzione anti-infiammatoria piuttosto che bloccare «semplicemente» l'azione delle citochine Th2

3. Ruolo nella genetica (miRNA) nell'identificare più correttamente nuovi endotipi per una medicina di precisione più avanzata

4. Disbiosi sinusale (*Novel microbiome-based therapeutics for chronic rhinosinusitis. Curr Allergy Asthma Rep 2015)*