Obstruktive lung disease and bronchiectasis in IEI – walking the line between eosinophilic to neutrophilic inflammation

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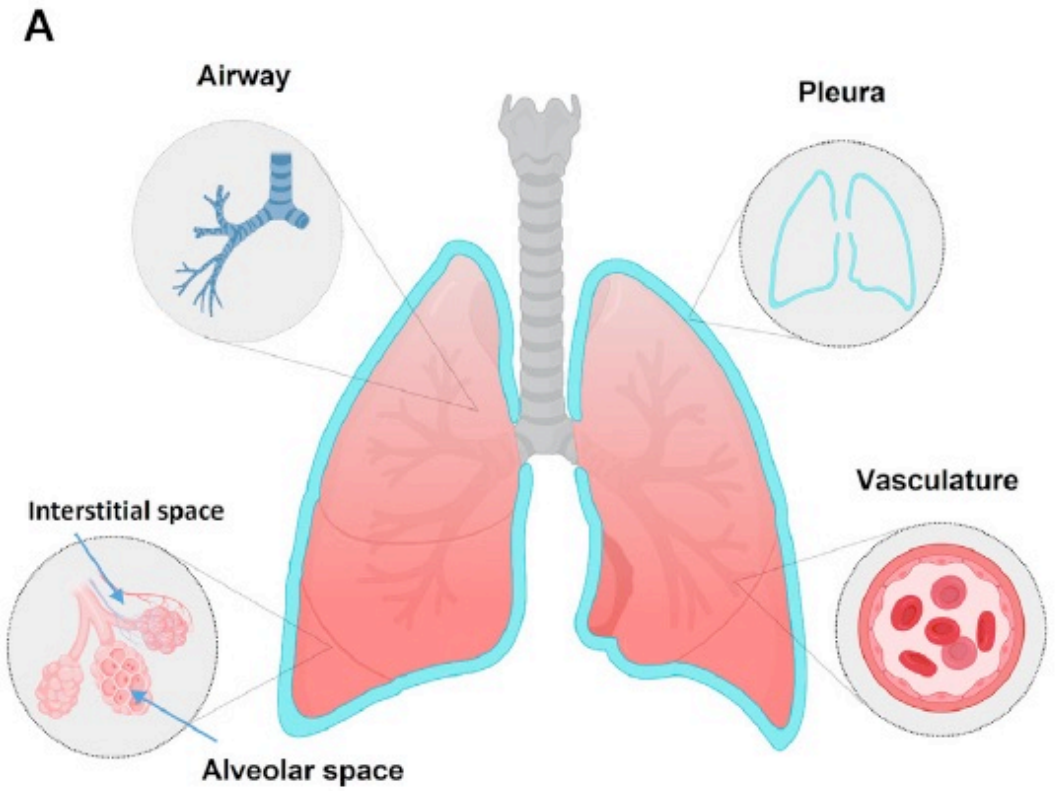
SLIPI 2023: XIII:e
Immunbristmöte

Båstad, 6-8 September 2023

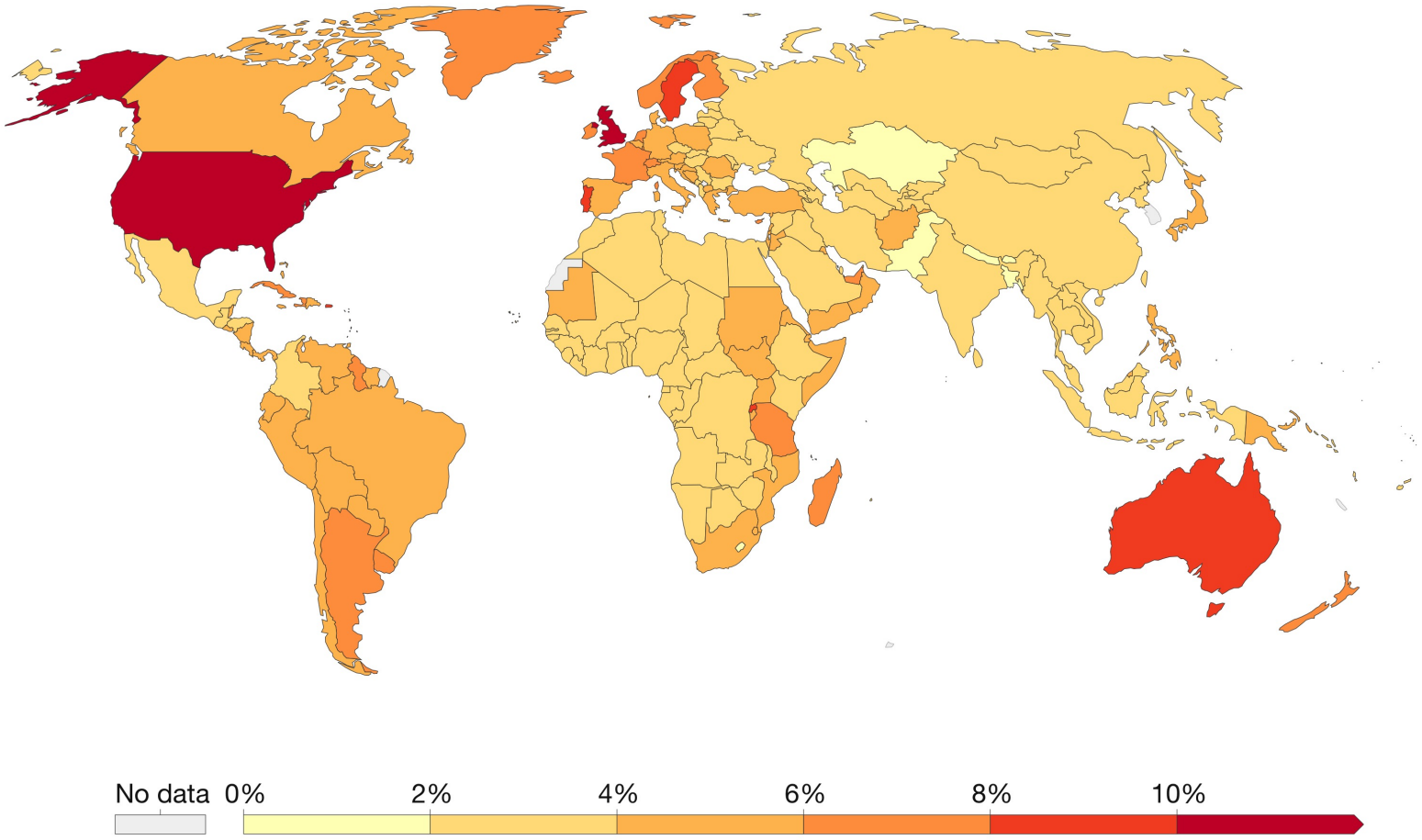
The lung in IEI

500ml x 14 breaths/min x 1440min =
10.080 liter / day

Size of a tennis court



Prevalence of Asthma worldwide



Asthma prevalence, 2019

The share of the population with asthma. Prevalence is age-standardized so accounts for changes in the age structure of a population over time and between countries.

Source: IHME, Global Burden of Disease

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Asthma*

Chronic inflammation of the airways.

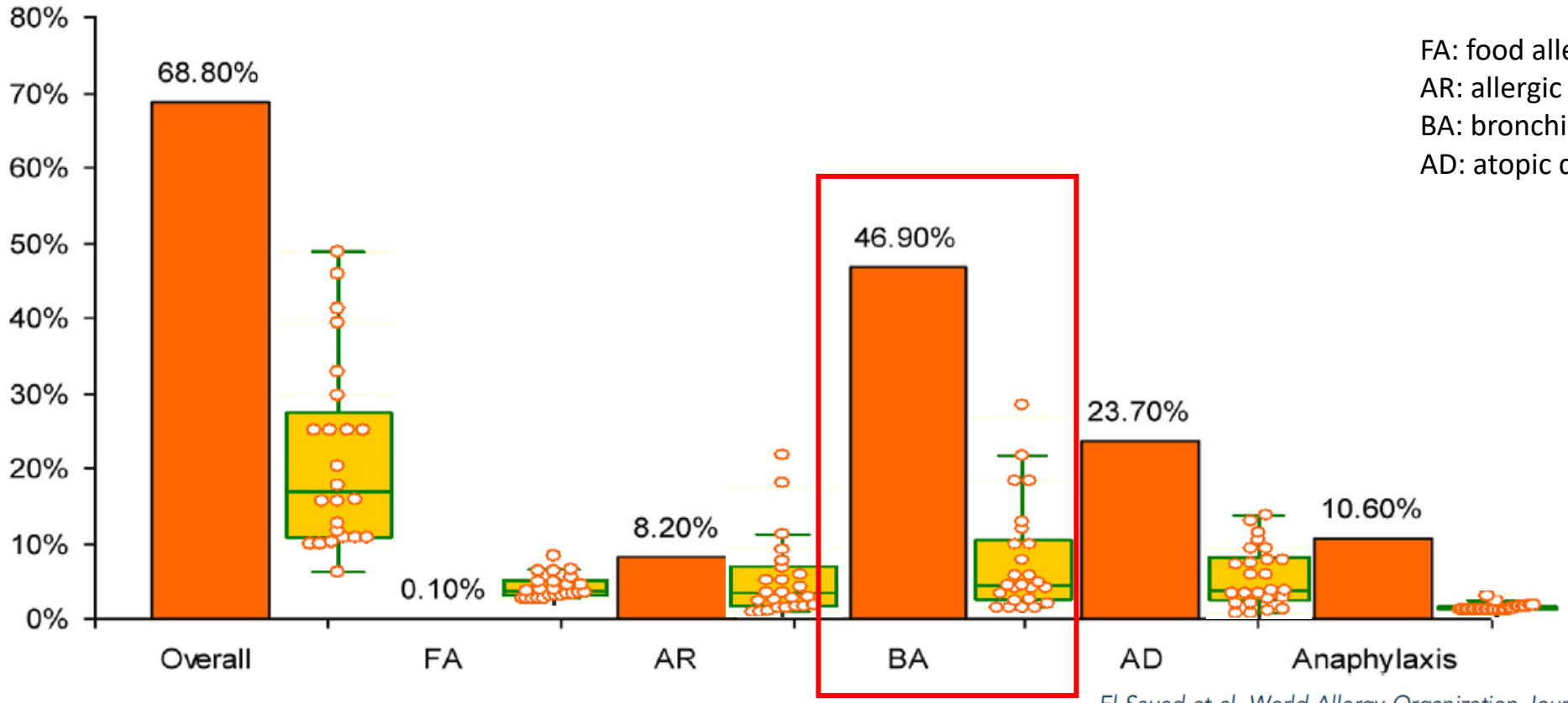
Clinic: wheeze, shortness of breath,
chest tightness, cough

Lung function:

- documented expiratory airflow limitation
  - Positive bronchodilator reversibility (>12% or >200ml from baseline) OR
  - Positive exercise challenge test (fall in FEV-1 of >10% and 200ml from baseline) OR
  - Positive bronchial challenge test (fall in FEV-1 >20% from baseline after methacholine or histamine)
- Documented excessive variability in lung function
  - average daily diurnal PEF variability > 10-13% OR
  - Variation in FEV-1 in lung function >12% and 200ml (outside of resp. infection)

- according to GINA (Global initiative for Asthma). www.ginasthma.org

Occurrence of atopic diseases in PID patients:



FA: food allergy
AR: allergic rhinitis
BA: bronchial asthma
AD: atopic dermatitis

Data from 30 different PID centers worldwide including 8450 adult and pediatric patients

Data from USIDNET registry including 2332 adult and pediatric patients

El-Sayed et al. World Allergy Organization Journal (2022) 15:100657

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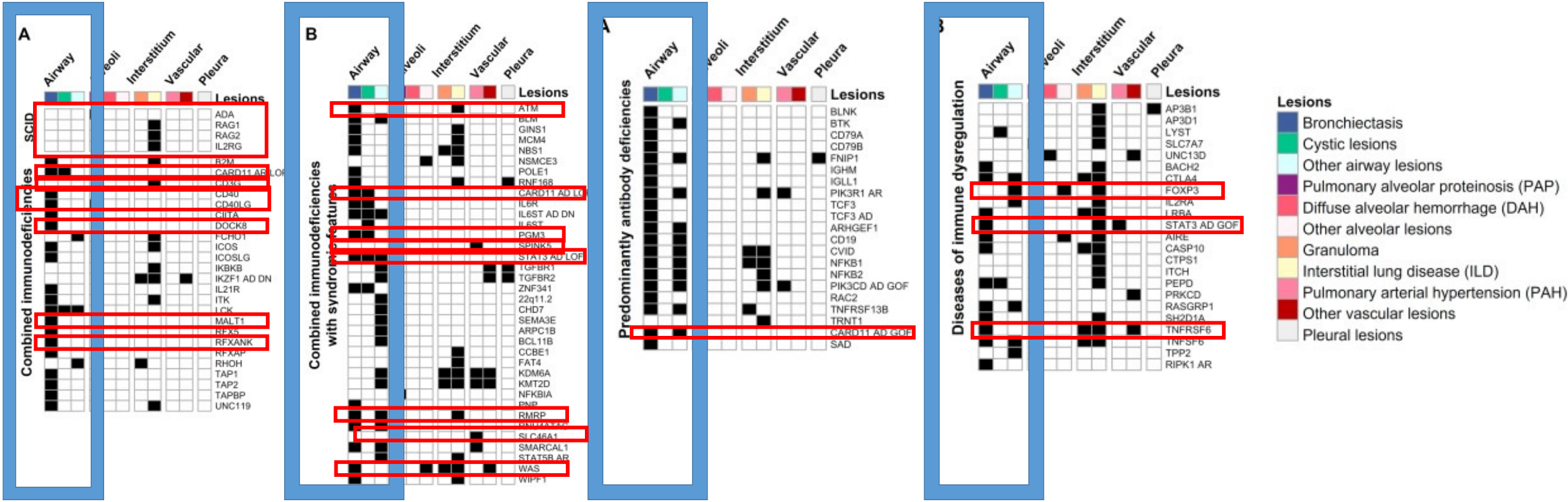
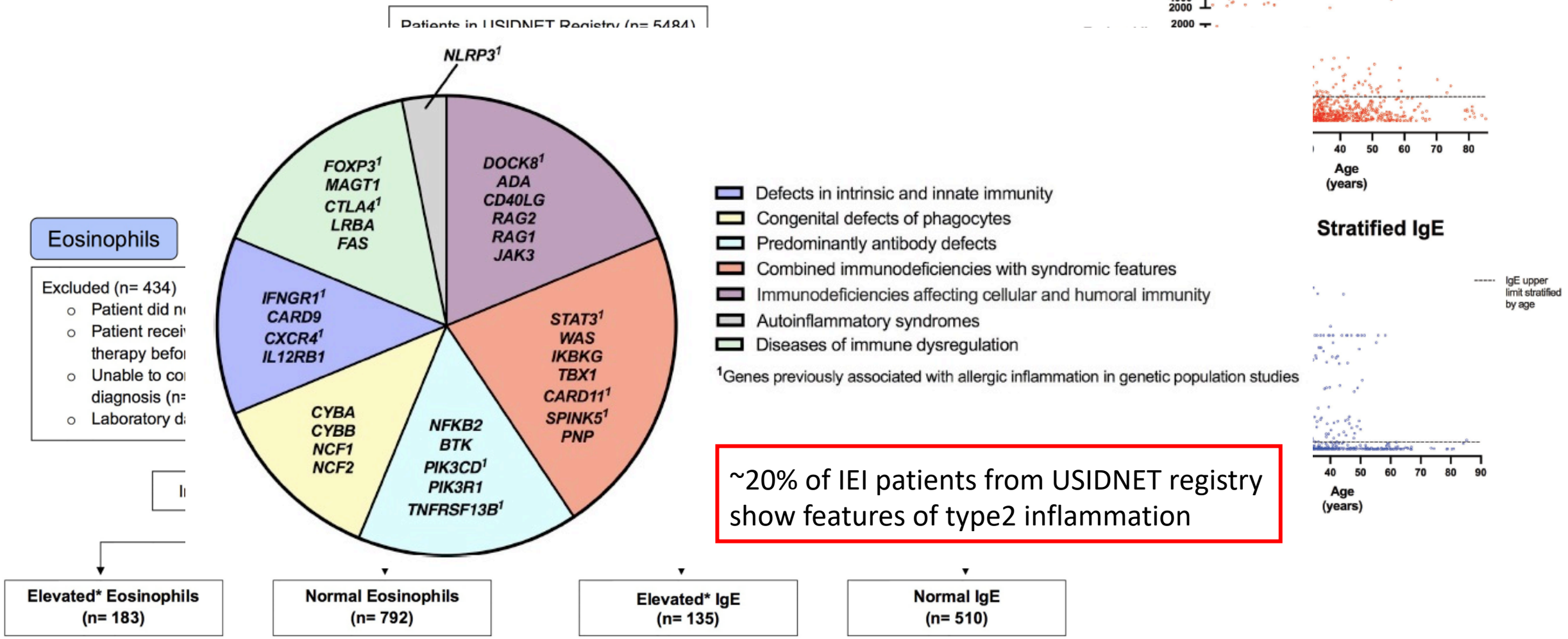
Pulmonary manifestations of IEI:



: IEI associated with eosinophilia

GUTIERREZ ET AL
J ALLERGY CLIN IMMUNOL
VOLUME 150, NUMBER 6

Type 2 inflammation in IEI:



~20% of IEI patients from USIDNET registry show features of type2 inflammation

Smith KL. Front. Immunol. 2022

Inhalative therapies in Asthma

Leukotriene modifiers, Biologicals

LAMA (long-acting muscarinic antagonists)

LABA (long-acting beta agonists)

ICS (inhalative corticosteroids)

BASIC

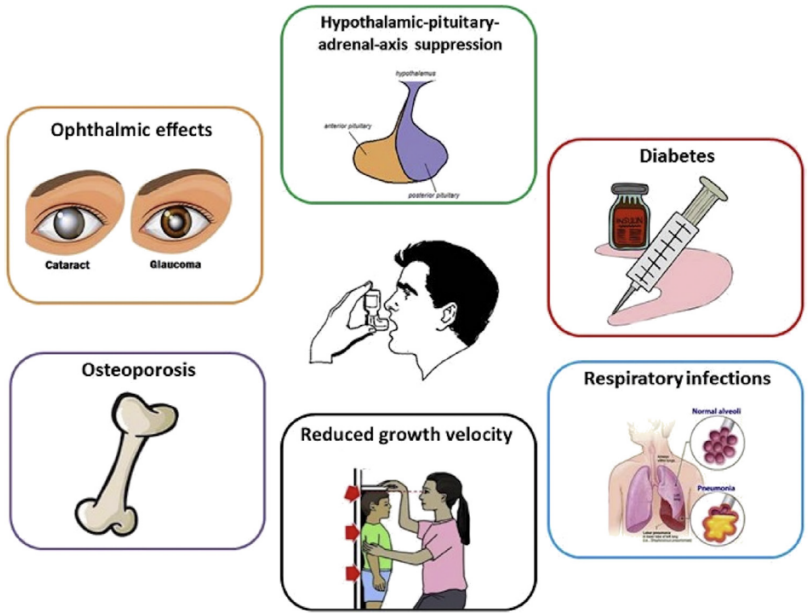


FIGURE 1. Common adverse effects related to the chronic use of inhaled corticosteroids.

Asthma difficult to treat usually express either:

- Very strong type 2 (eosinophilic) inflammation
- Neutrophilic inflammation

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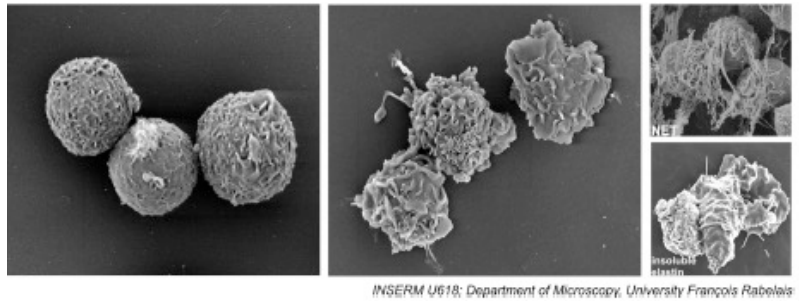
J Allergy Clin Immunol Pract 2018;6:776-81

Neutrophilic and eosinophilic inflammation in asthma:

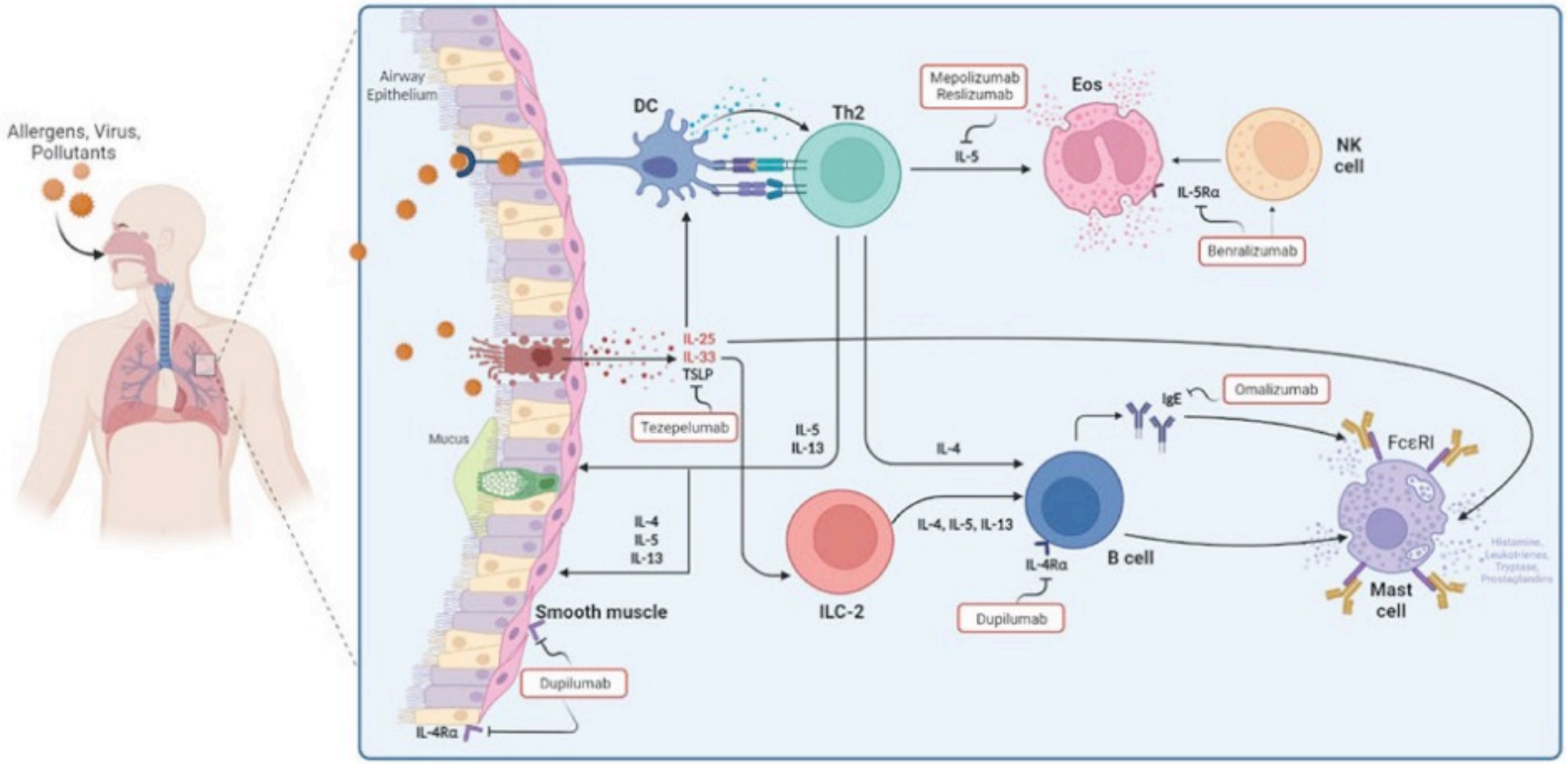
50%

50%



INSERM U618; Department of Microscopy, University François Rabelais

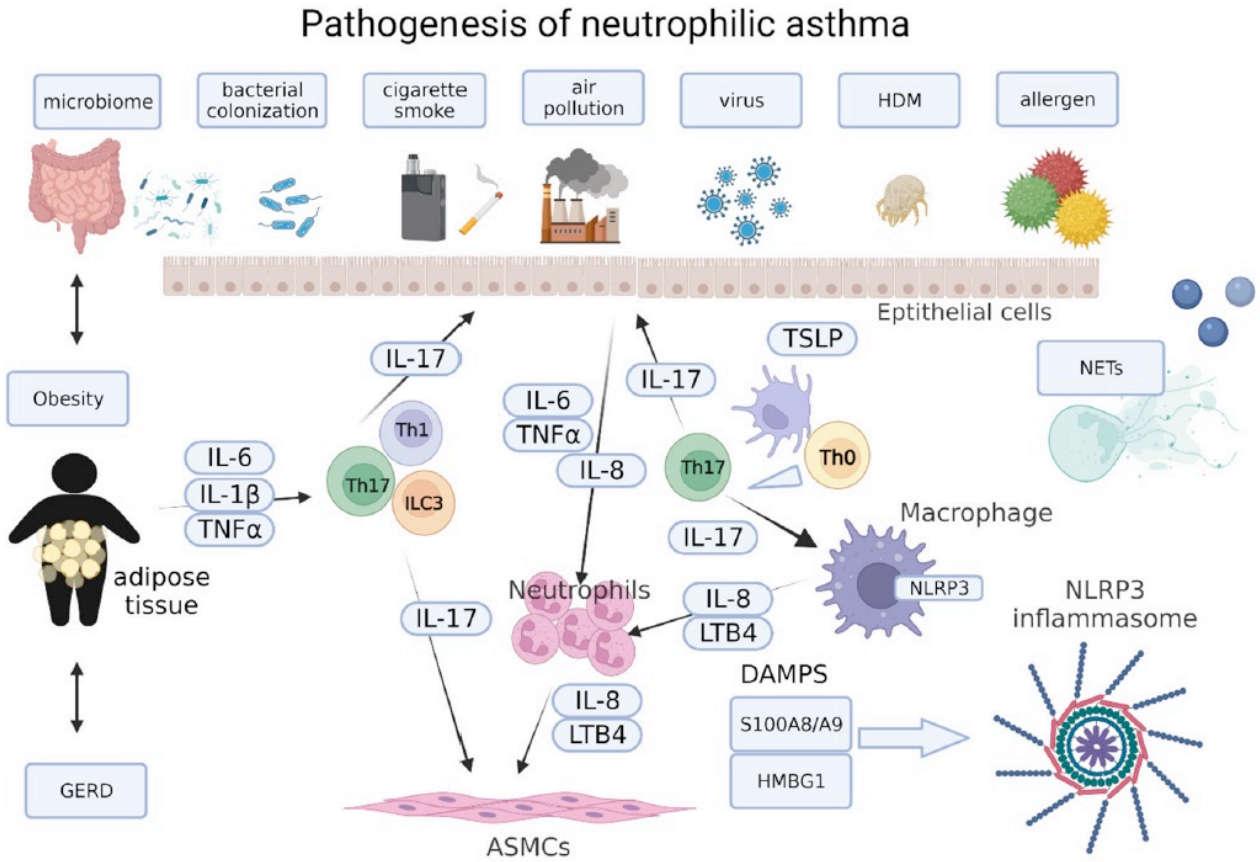
Eosinophilic / type 2 inflammation:



Pharmaceuticals **2023**, *16*, 270

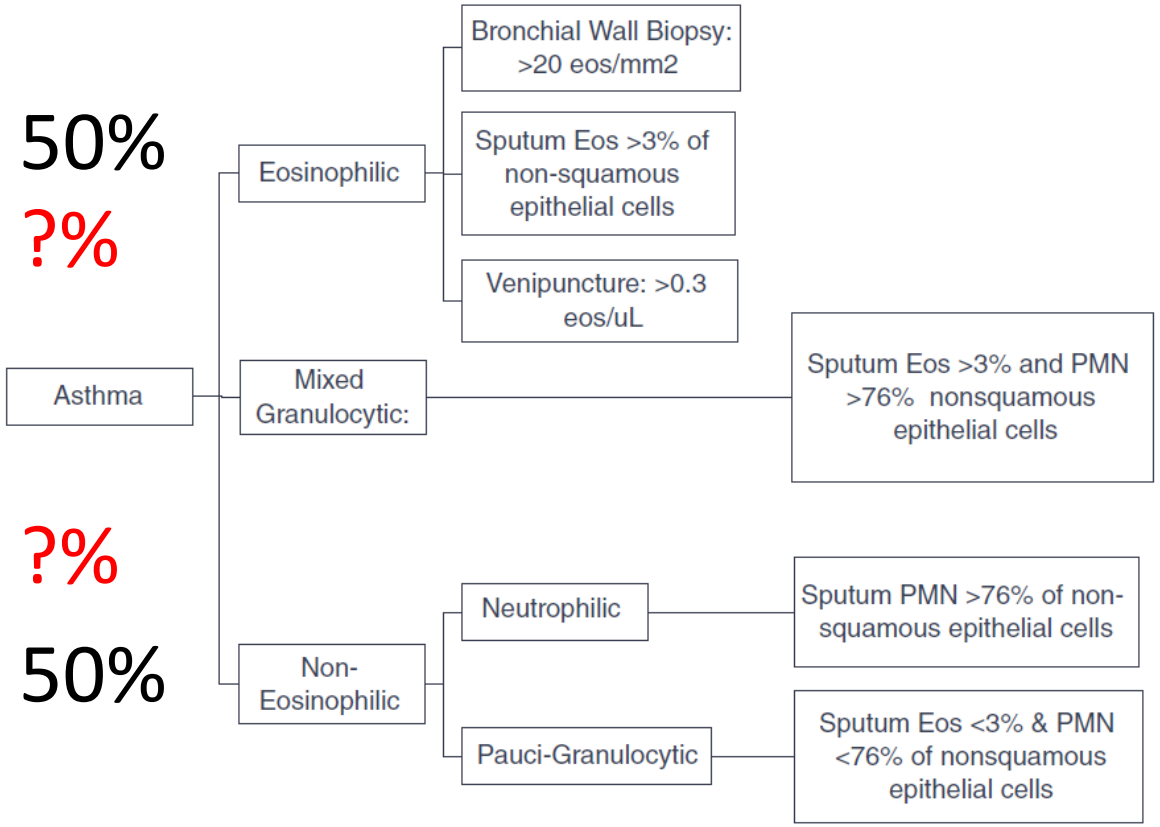
Neutrophilic (non-eosinophilic) inflammation:

- Steroid-resistent
- Late onset
- More often in obese patients
- Related to smoking



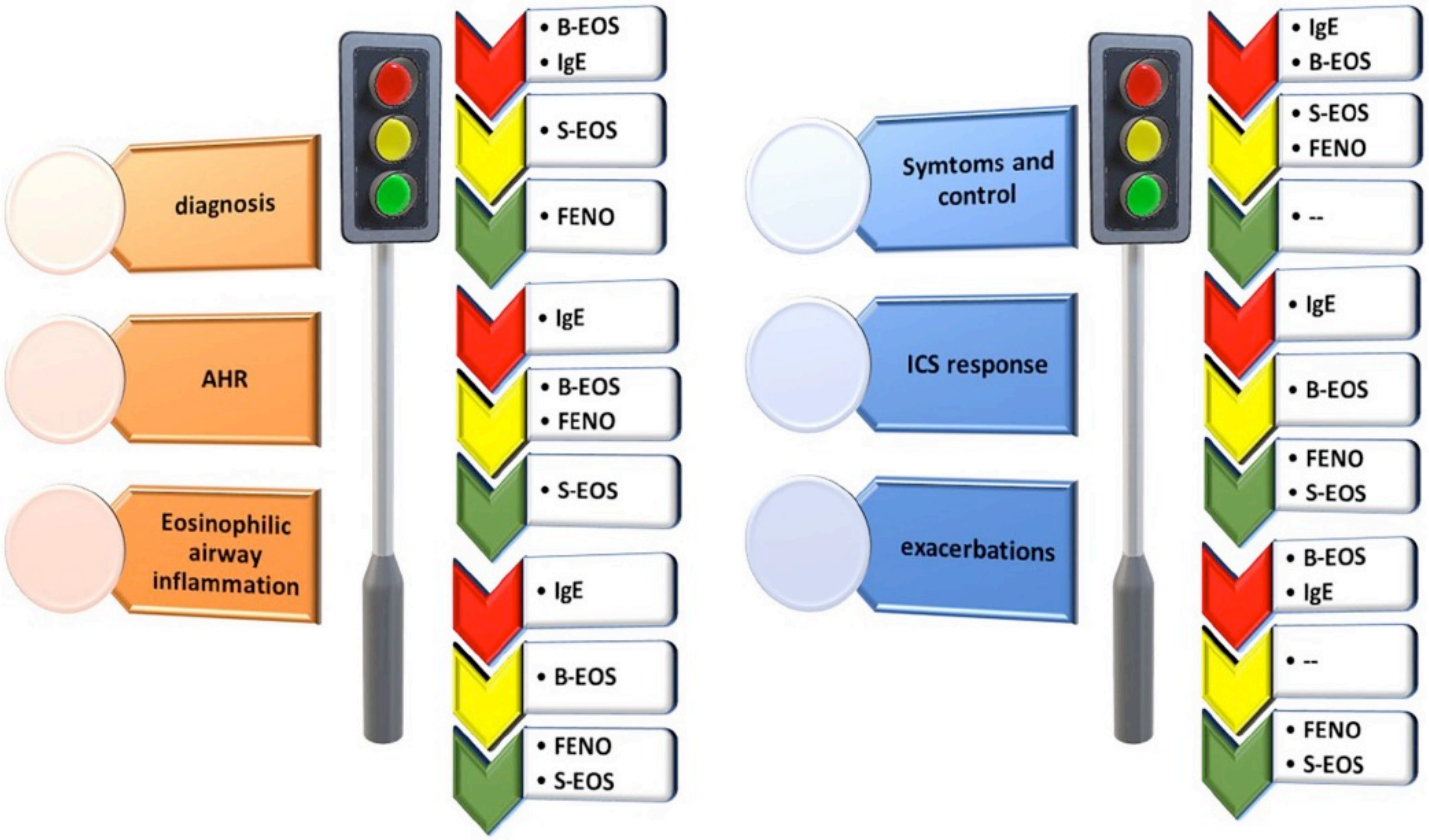
Harada, T. Neutrophils and Asthma. *Diagnostics* **2022**, *12*, 1175.

Eosinophilic and non-eosinophilic inflammation of Asthma in IEI patients:



Asthma in the 21st Century. DOI: https://doi.org/10.1016/B978-0-323-85419-1.00005-0

Biomarkers of type 2 inflammation: What and where to look at?



Blood eosinophils?

Sputum eosinophils?

IgE in serum?

Blood neutrophils?

Cytokines in sputum?

Serum periostin?

Eosinophil-derived Neurotoxin?

Front. Med. 9:969243.

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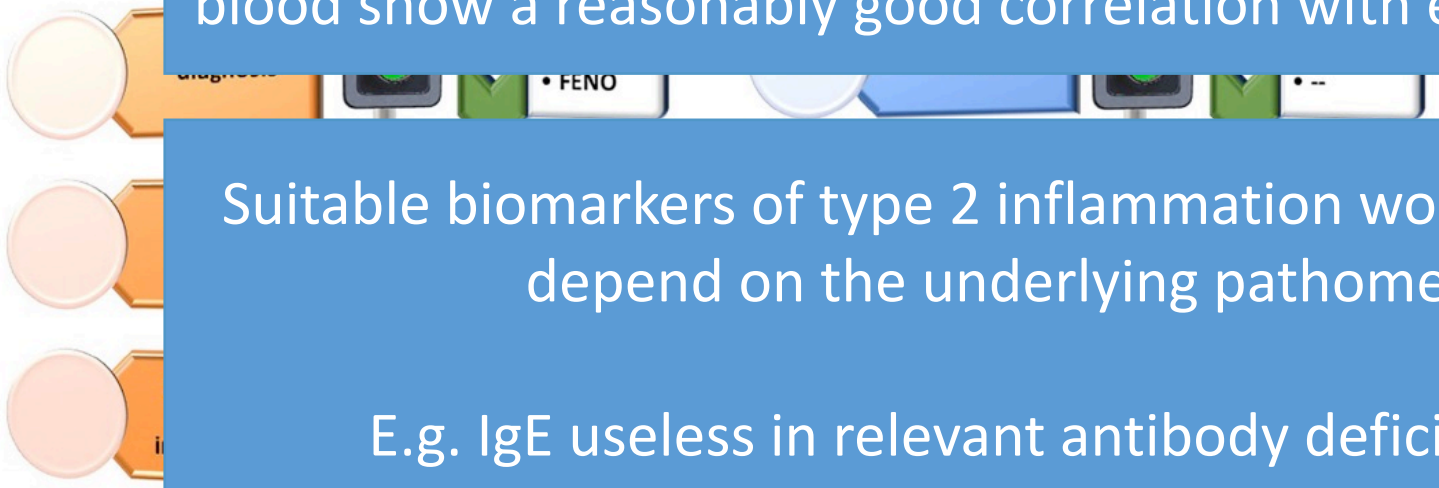


In systemic inflammatory disorders levels of eosinophils in peripheral blood show a reasonably good correlation with eosinophils in sputum.

Suitable biomarkers of type 2 inflammation work in patients with IEI depend on the underlying pathomechanism.

E.g. IgE useless in relevant antibody deficiency disorders.
Role and correlation of eosinophils in blood, sputum and tissue need to be established.
Intracellular cytokine staining of IL-4, IL-5 may work?

ls?

m?

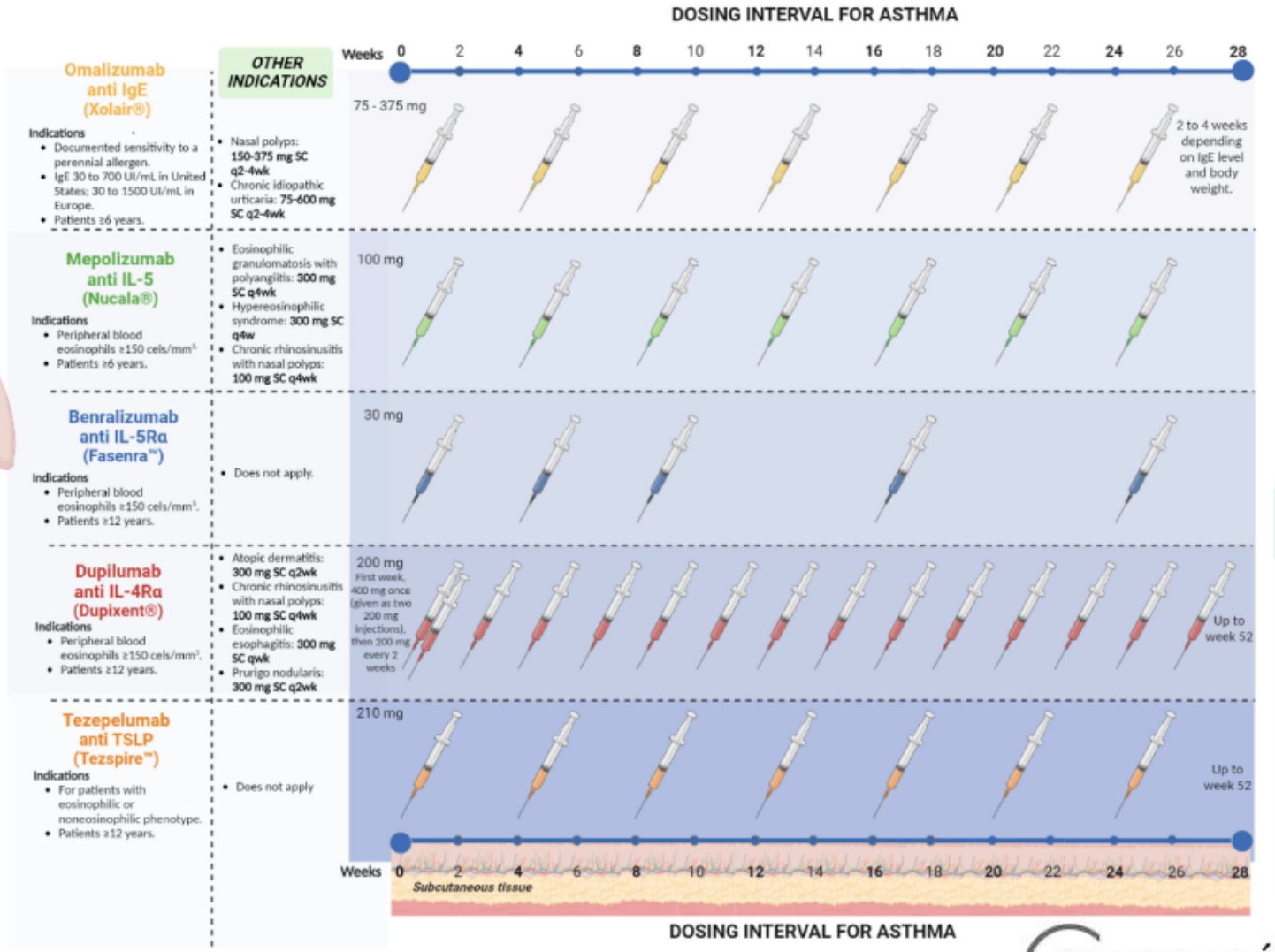
Neurotoxin?

Front. Med. 9:969243.

Biologics in Asthma treatment:

GLOBAL INDICATION FOR ASTHMA

Incomplete symptom control with high-dose inhaled glucocorticoid therapy.



CLINICAL OUTCOMES FOR ASTHMA

Reduce asthma exacerbations.

Improve lung function.

Reduce oral corticosteroid use.

Improve quality of life.

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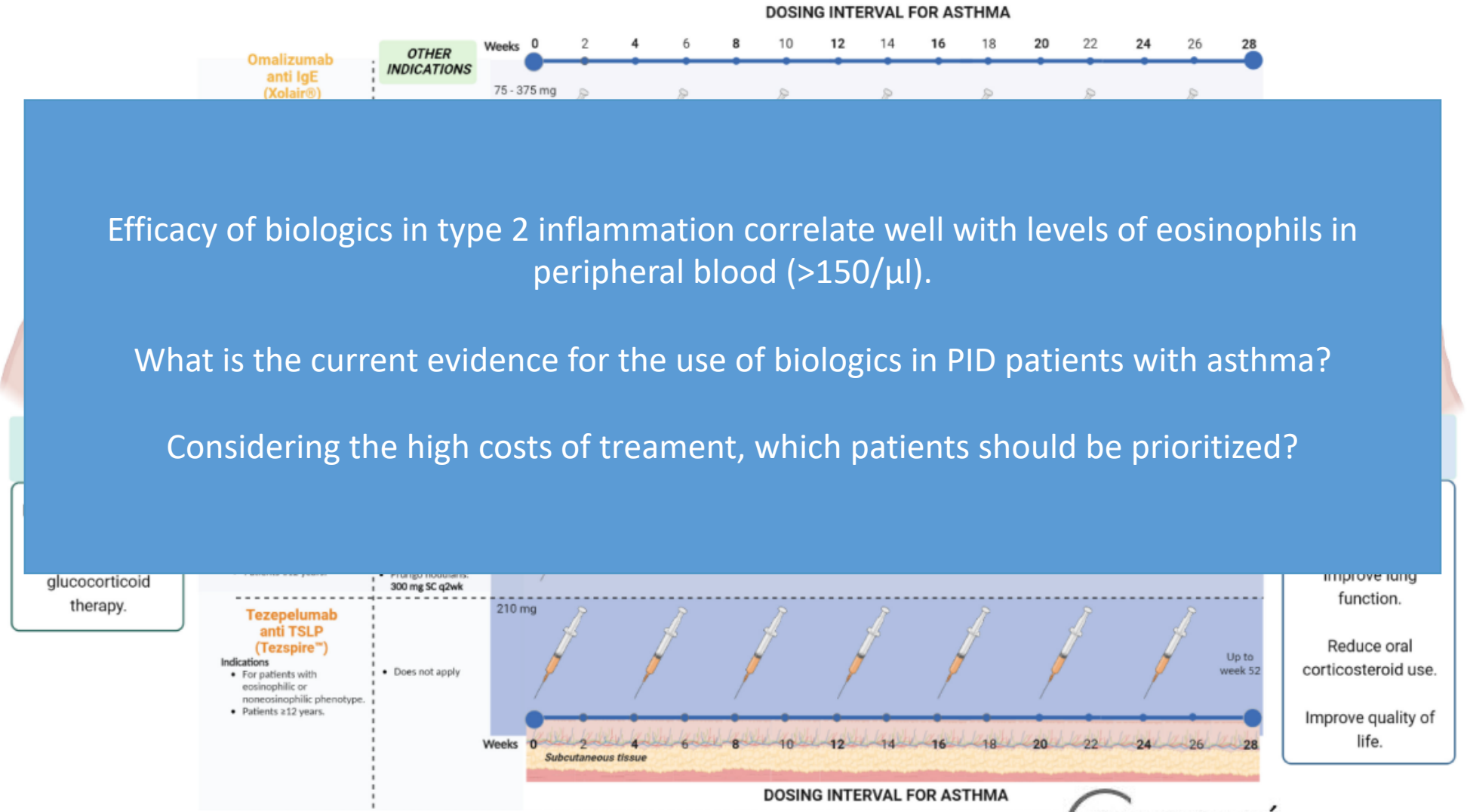
Biologics in Asthma treatment:



Efficacy of biologics in type 2 inflammation correlate well with levels of eosinophils in peripheral blood (>150/µl).

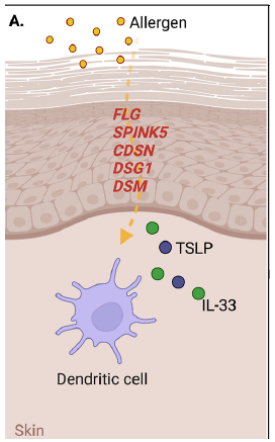
What is the current evidence for the use of biologics in PID patients with asthma?

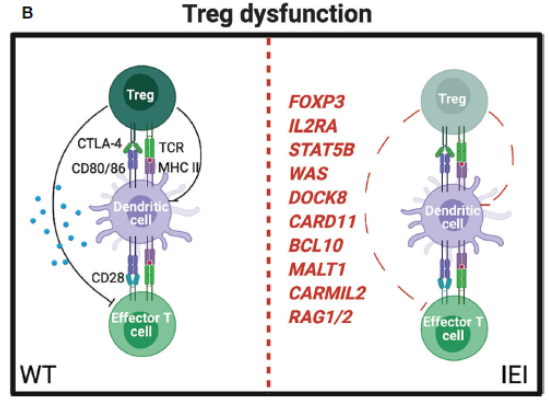
Considering the high costs of treament, which patients should be prioritized?

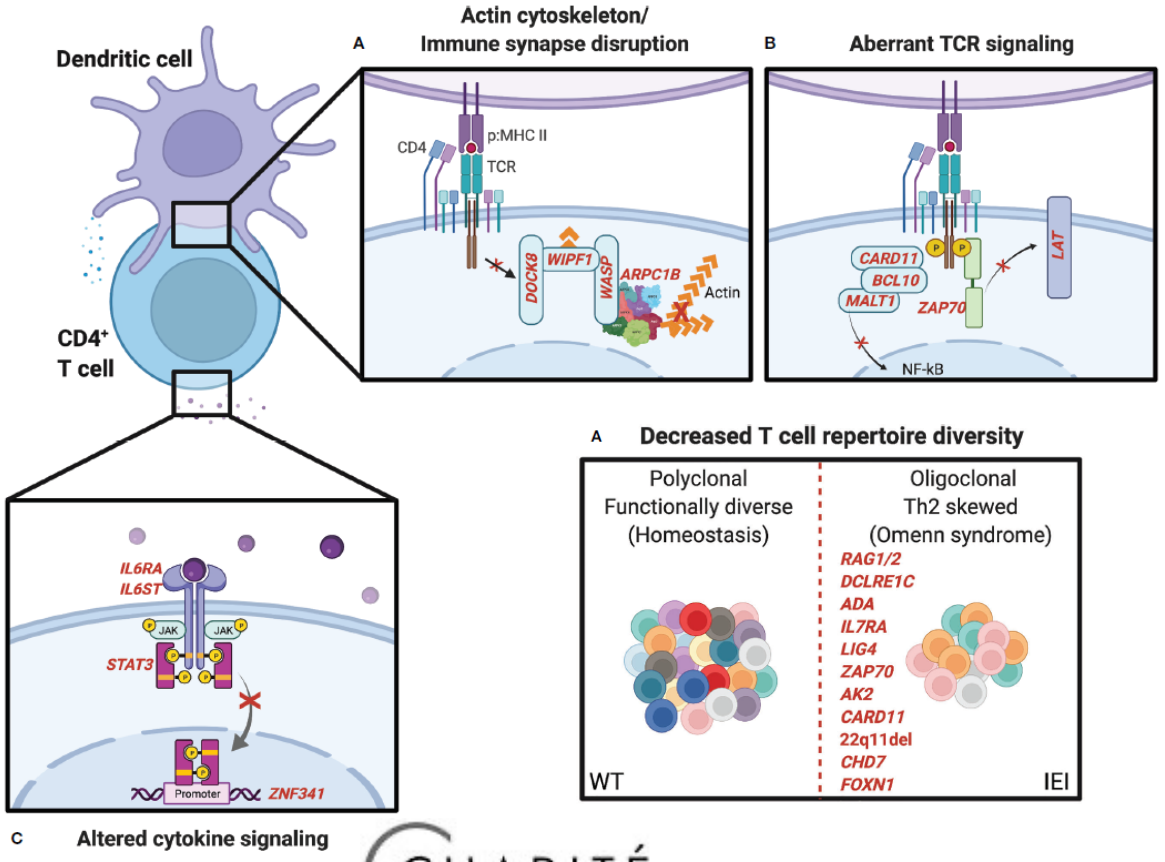
Pharmaceuticals **2023**, *16*, 270

Linking atopic disease with IEI

- disorders of barrier function
- decreased T-cell receptor repertoire
- regulatory T cell (Treg) dysfunction
- cytoskeletal abnormalities
- aberant TCR signaling
- altered cytokine signaling







Nelson RW, Front Immunol 2022

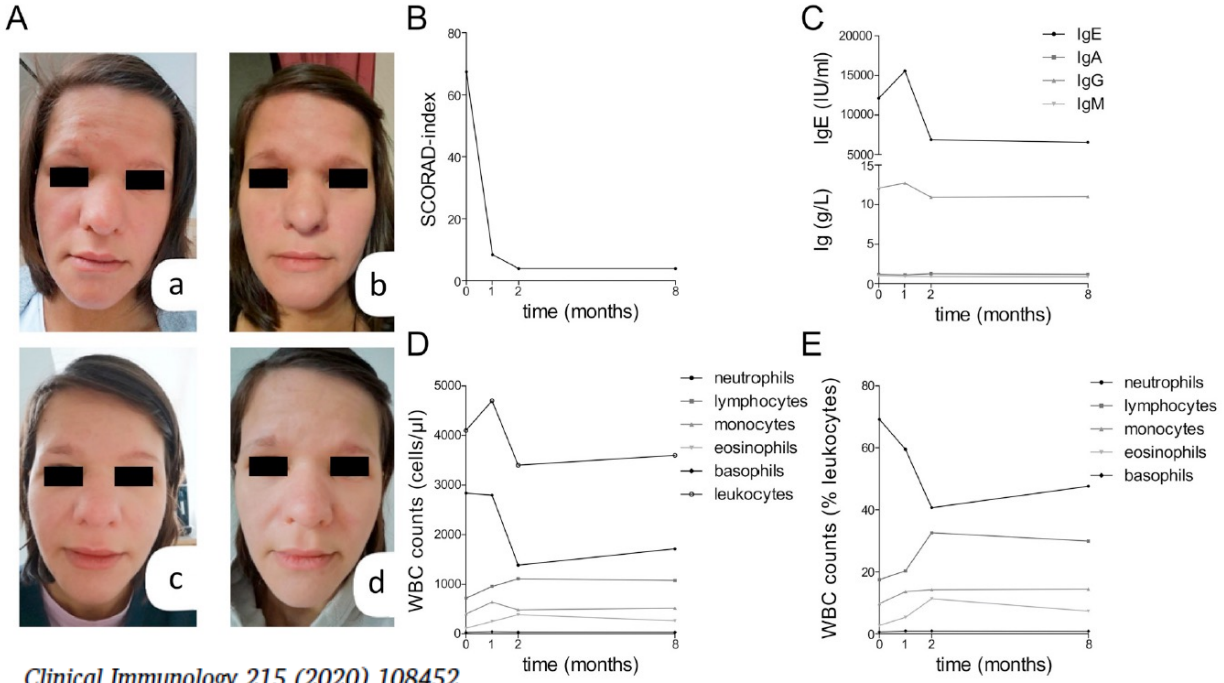
Evidence for specific treatment of type 2 inflammation in IEI:

"So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown" Job 2:7

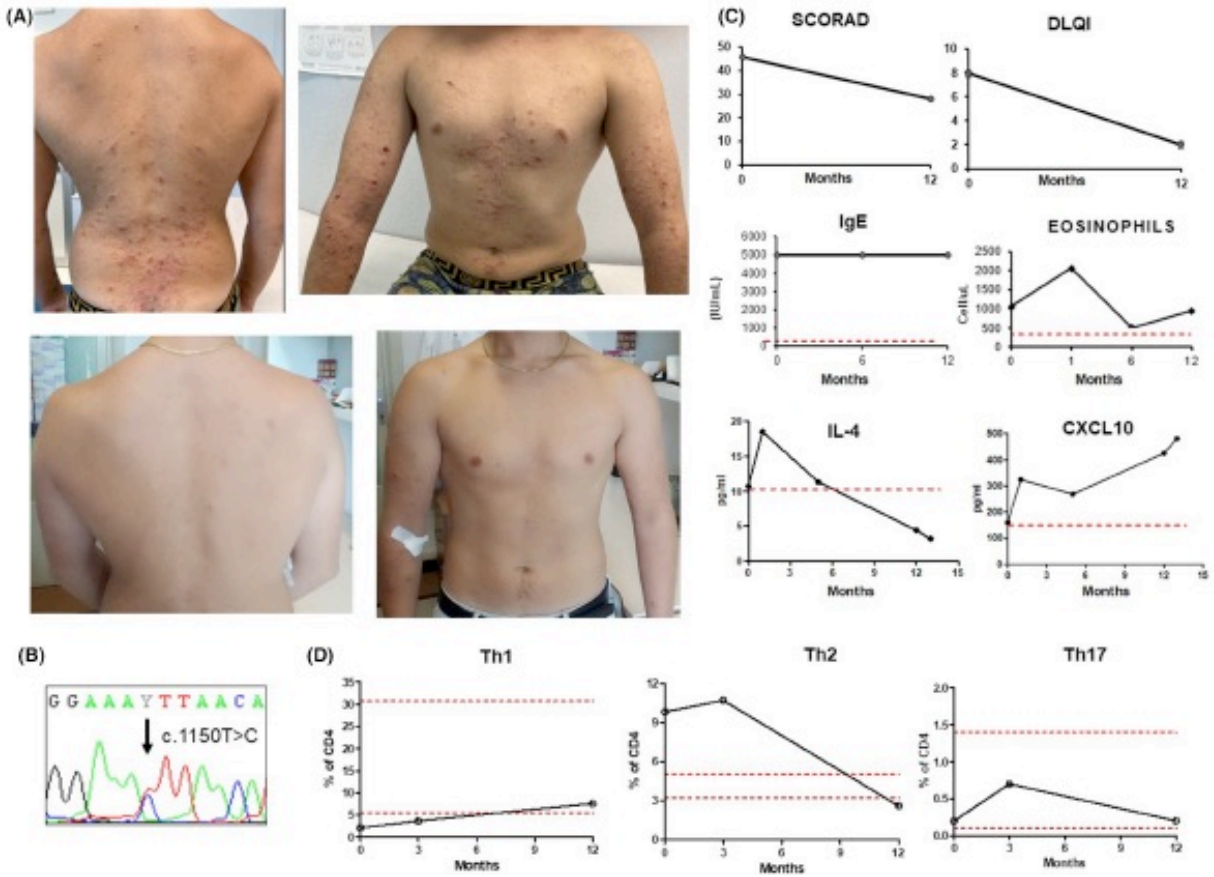
Very few case reports on patients with AD HIES (STAT3 LOF):

Dupilumab: 7x
Omalizumab: 2x
Mepolizumab: 0
Benralizumab: 0

Use of Dupilumab (anti-IL-4/IL-13) in AD HIES:



Clinical Immunology 215 (2020) 108452



Pediatr Allergy Immunol. 2022;33:e13770.

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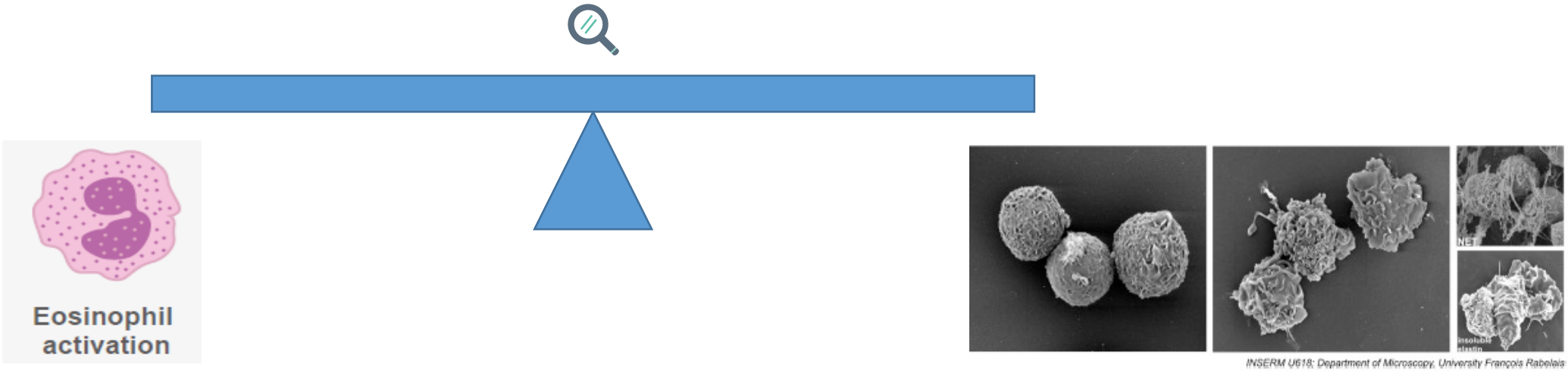
Neutrophilic and eosinophilic inflammation in asthma:



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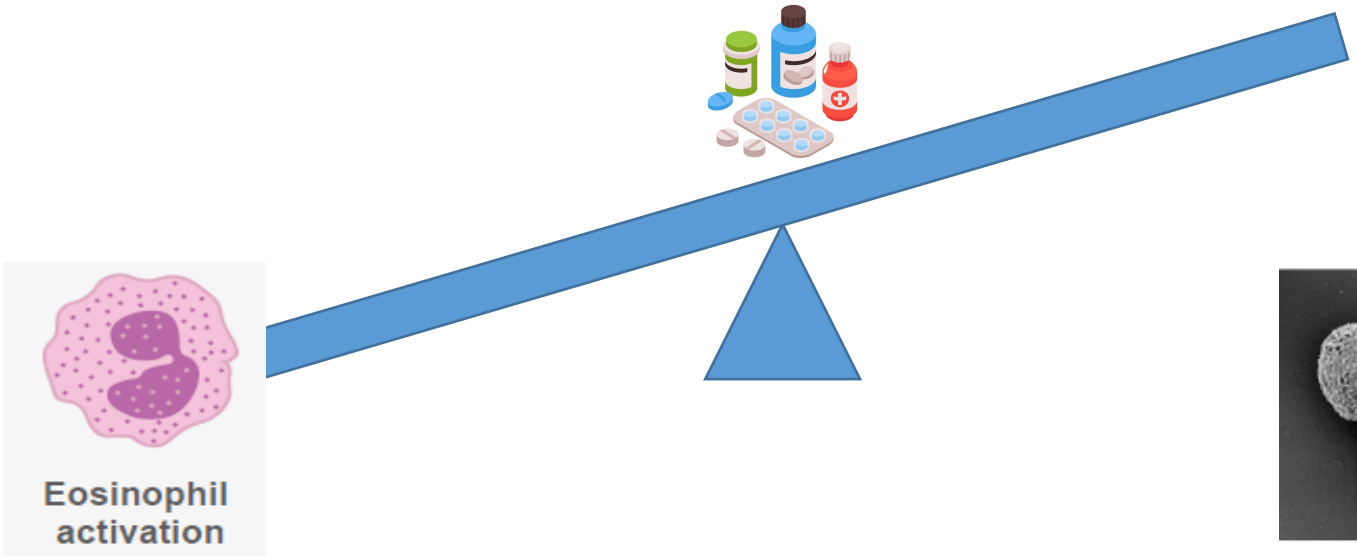

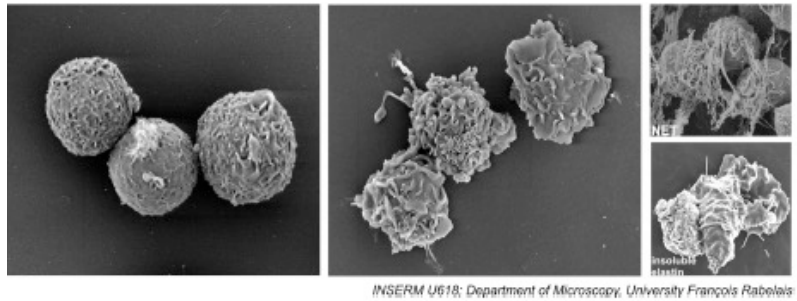

- underlying pathomechanisms are well defined in IEI patients
- Increasing knowledge on the type of inflammation in IEI
- clinical evidence and experiences of different treatments are still very limited in IEI

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monogenic versus polygenic

IEI

Allergy?

Monogenic:	Polygenic:
high genetic contribution	low genetic contribution
single mutation in one gene	hundreds of variants in many genes
large genetic effect	each variant has a small genetic effect
rare	common
high penetrance	low penetrance
no or very small environmental influence	environment is a key determinant

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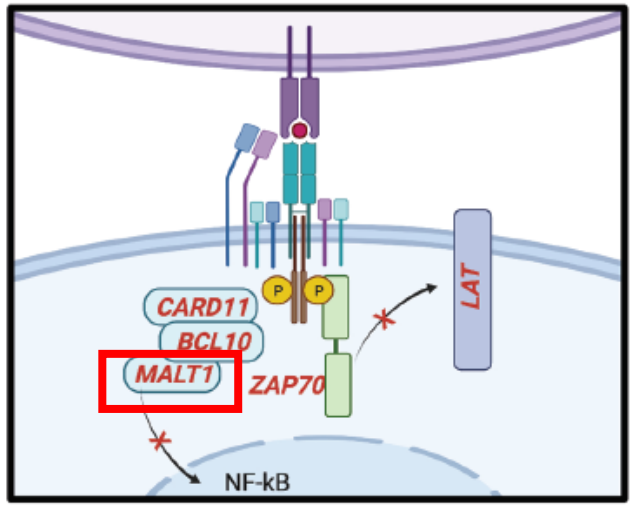
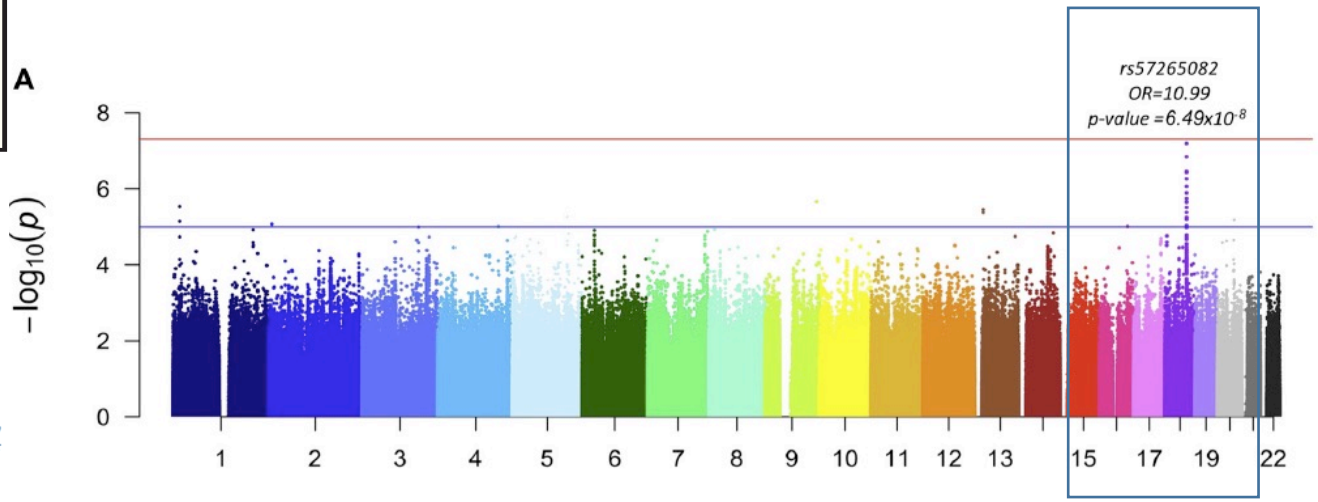
The NEW ENGLAND JOURNAL of MEDICINE

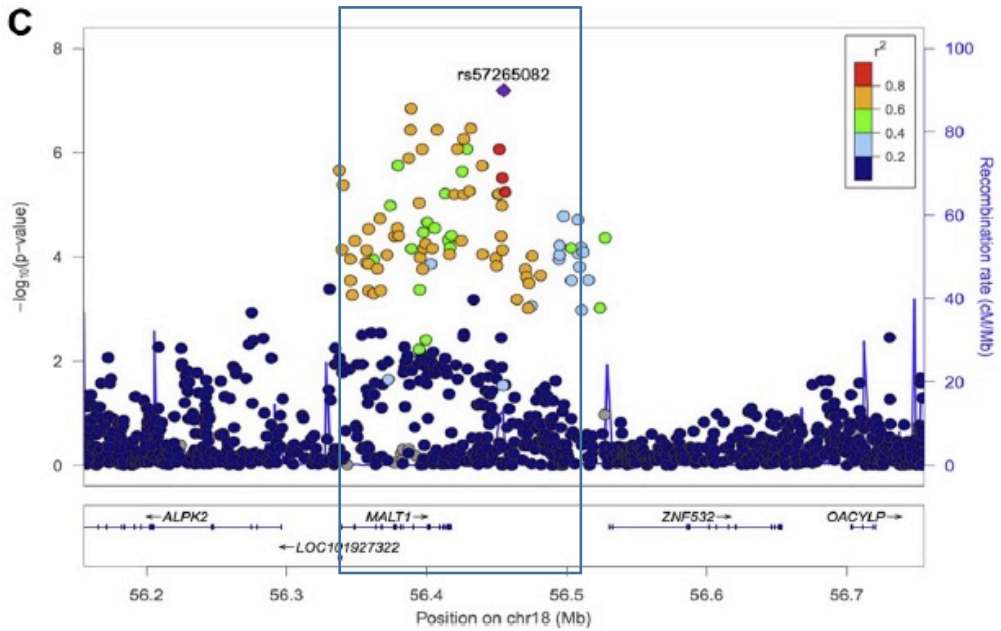
ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*







Toit G *et al. N Engl J Med.* 2015;372(9):803–813.
Winters A *et al. JACI.* 2019;143(6):2326–2339.
Nelson R *et al. Front Immunol.* 2022;27;13:860821.

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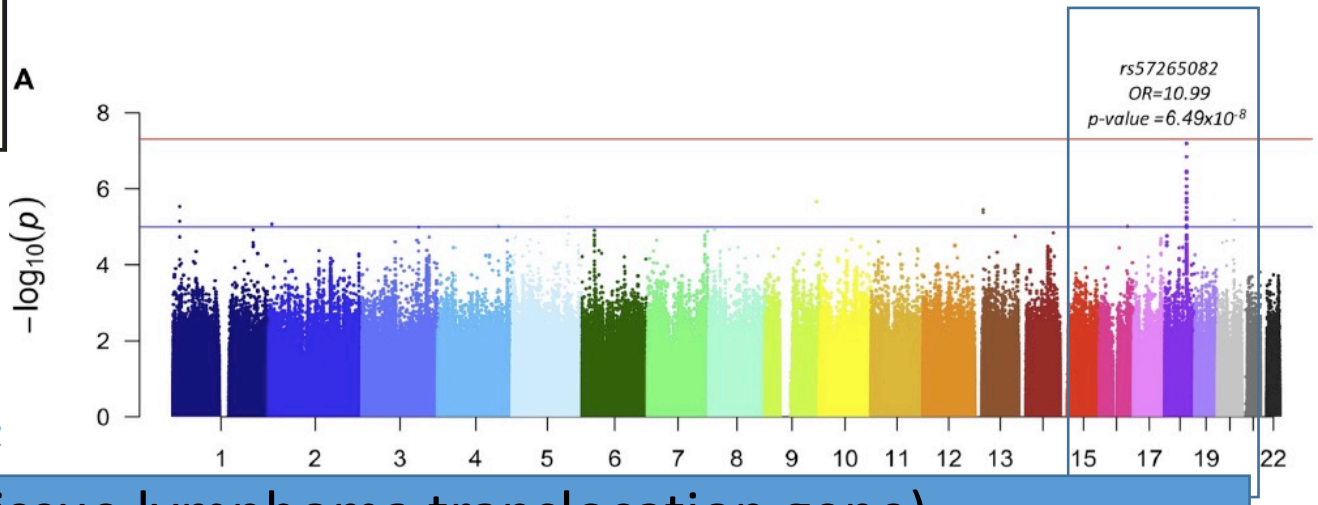
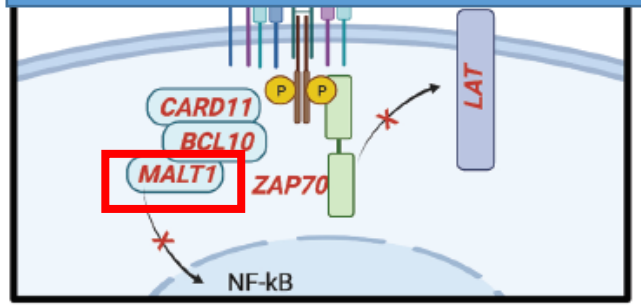
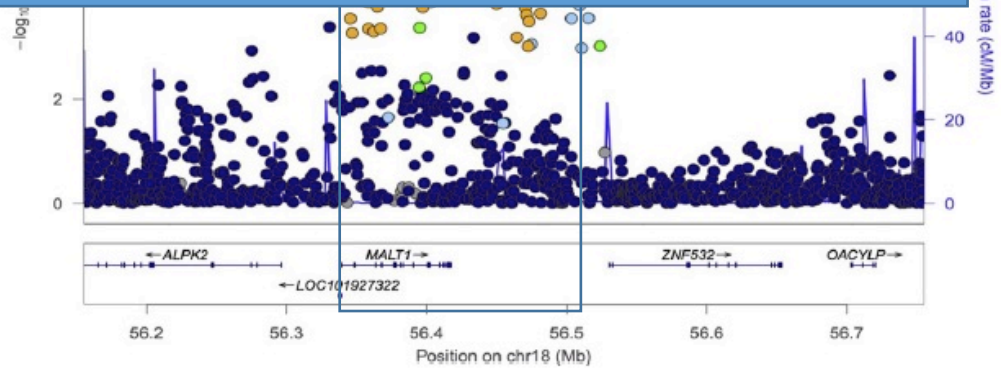


MALT1 (mucosa-associated lymphoid tissue lymphoma translocation gene) :

AR disorder: (S)CID with high IgE and eosinophilia

MALT1 rs57265082: carriers in the avoidance group were at increased risk for developing peanut allergy (OR 11)





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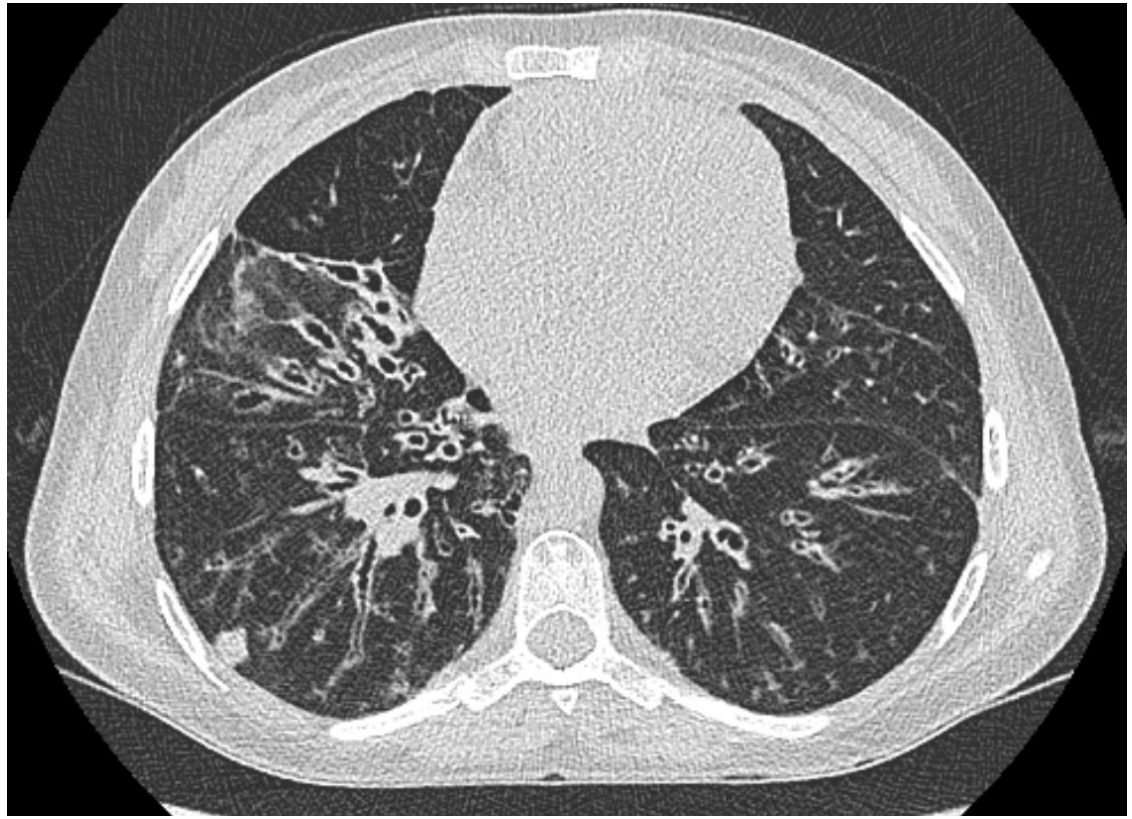
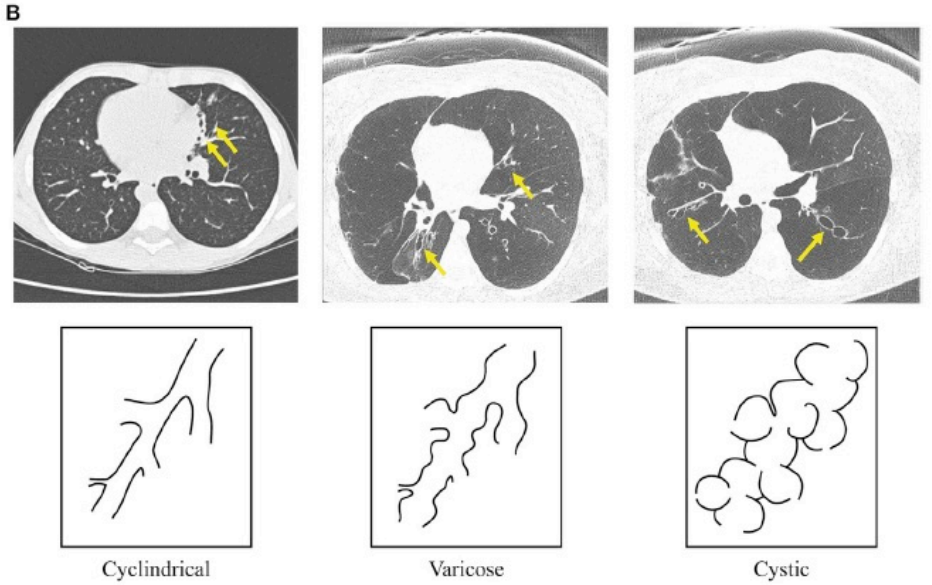
Winters A *et al. JACI.* 2019;143(6):2326–2339.
Nelson R *et al. Front Immunol.* 2022;27;13:860821.

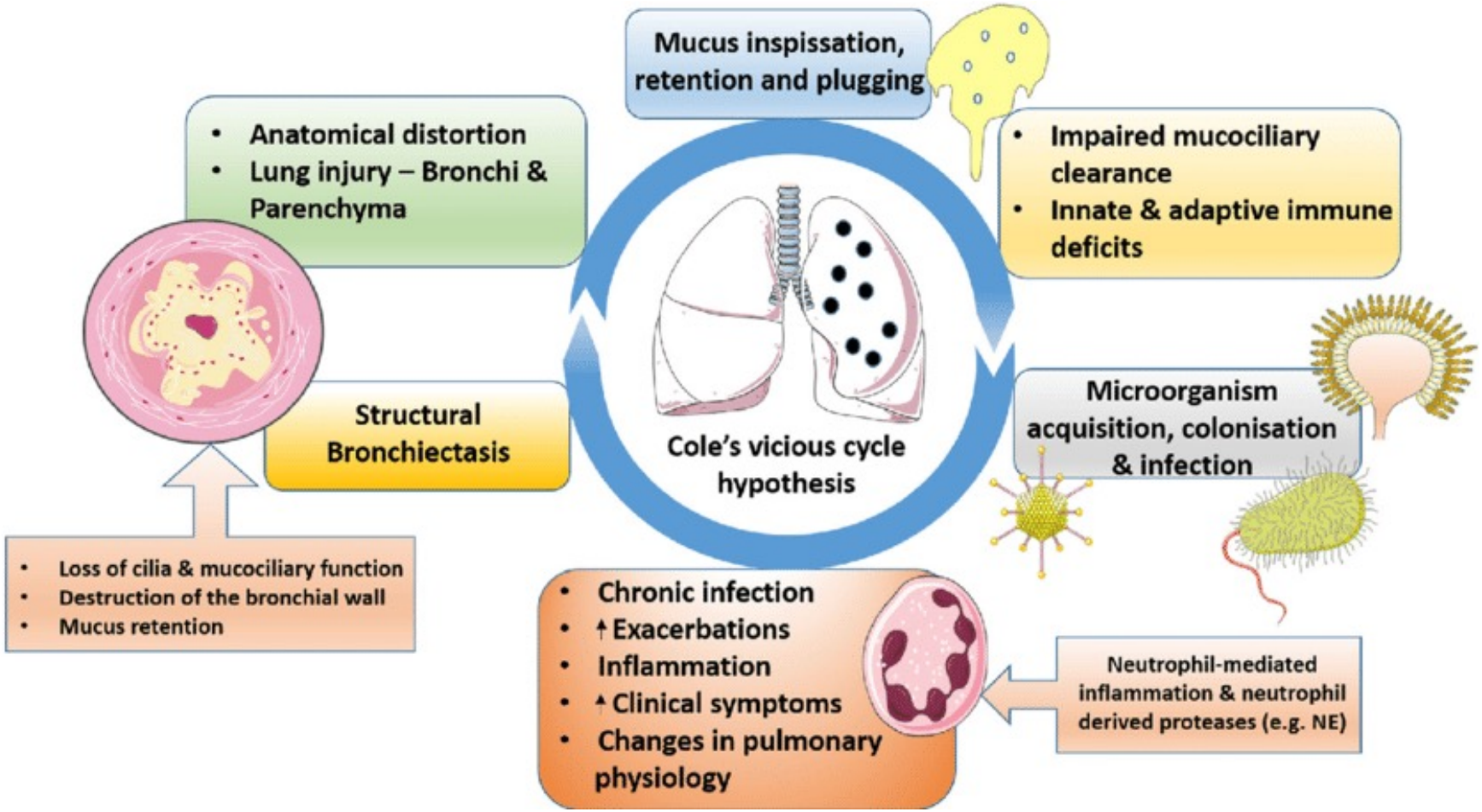
Persistent respiratory trouble? Don‘t stop looking…



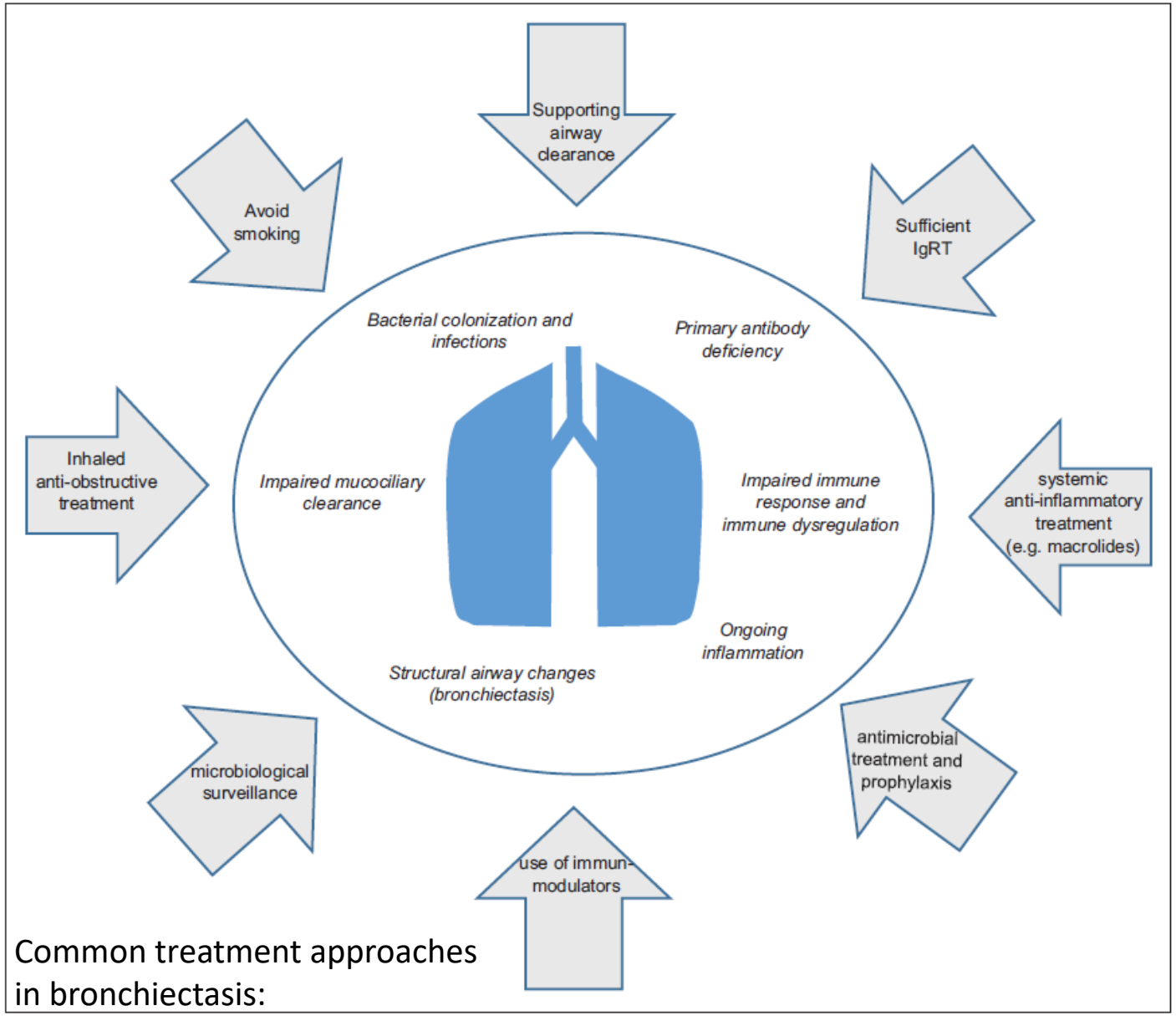


Curr Opin Allergy Clin Immunol. 2022 Dec 1;22(6):335-342.

Bronchiectasis:



Chandrasekaran *et al. BMC Pulmonary Medicine* (2018) 18:83
https://doi.org/10.1186/s12890-018-0638-0



Common treatment approaches in bronchiectasis:

Curr Opin Allergy Clin Immunol. 2022 Dec 1;22(6):335-342

Airway clearance in (non-CF) bronchiectasis:

- Any physical exercise helps
- Offer physiotherapy
- Encourage to clear the lungs
- Metaanalysis on inhalation of (hypertonic) saline solution is does not favour 0,9% vs. 3% vs. 6%
- Expectorants (NAC) or Mannitol inhalation show no clear benefit
- Negative data for DNase

O'Donnell AE et al. Chest. 1998; 113(5).

Xie B et al. Am J Emerg Med. 2020 Dec;38(12):2713-2717

Bilton D et al. Thorax. 2014 Dec;69(12):1073-9.

Bilton D et al. Chest. 2013 Jul;144(1):215-225.

Use of macrolides in PAD and in COPD

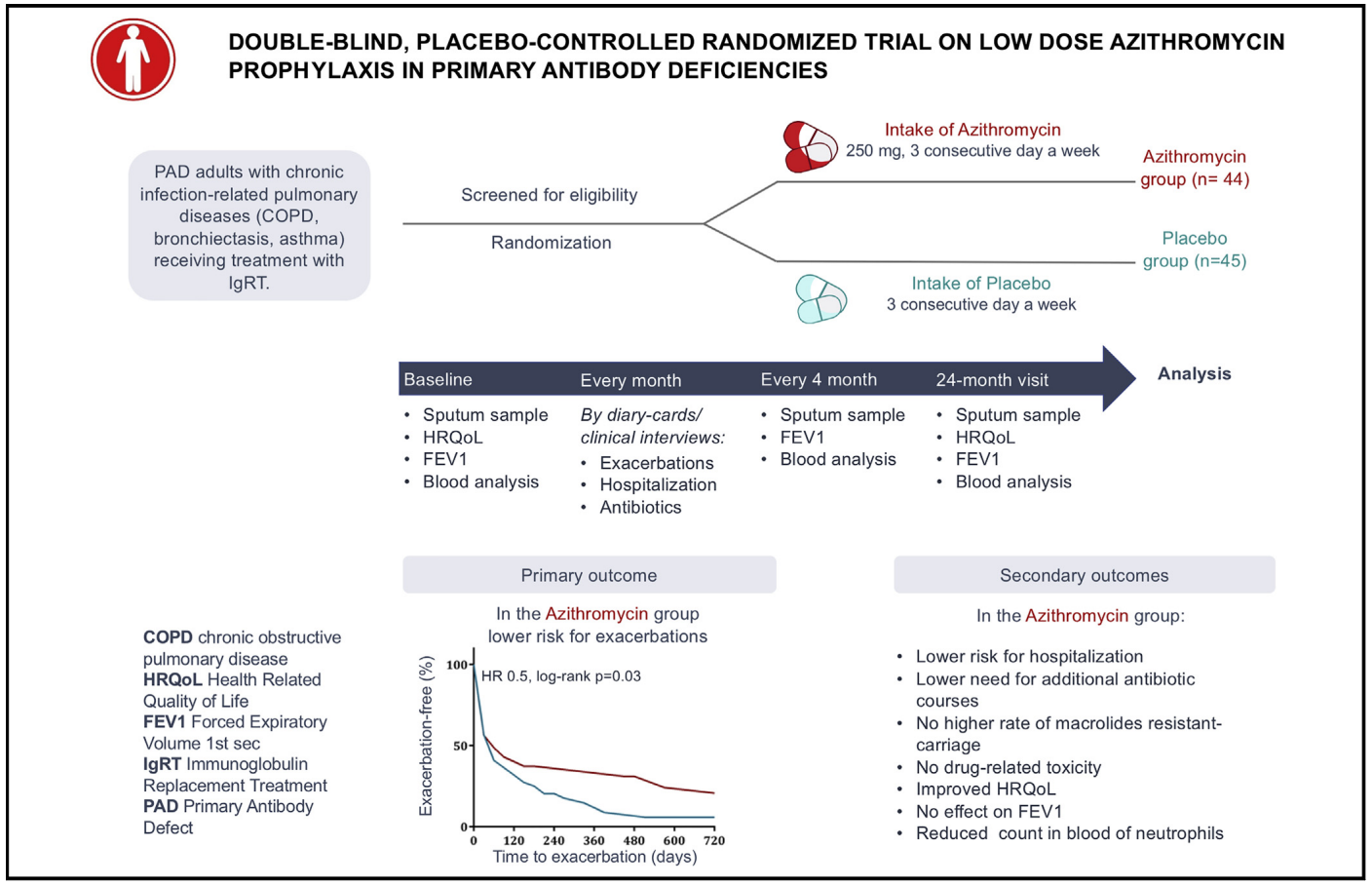
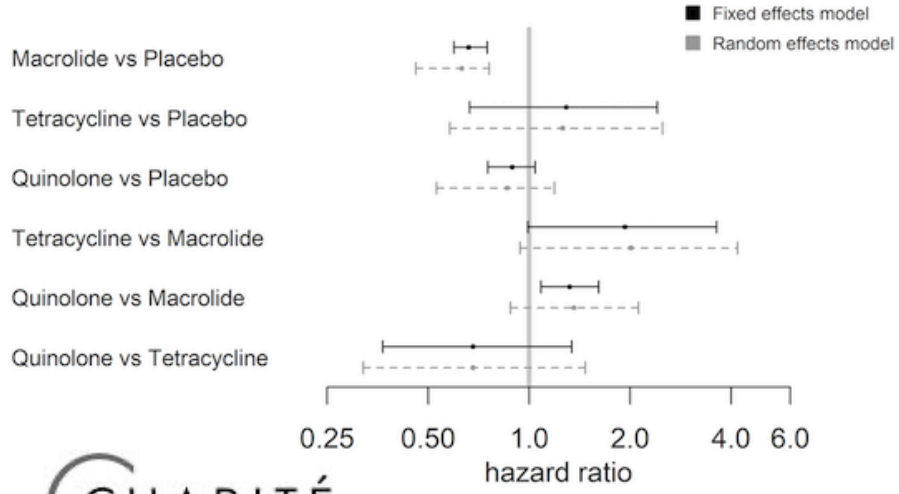


TABLE II. Baseline characteristics of the intention-to-treat population

	Azithromycin (n = 44)	Placebo (n = 45)	*P* value
Age (y), mean (SD)	45.0 (14.9)	45.0 (14.0)	.895
Sex, no. (%)			
Female	23 (52)	26 (58)	.602
Male	21 (48)	19 (42)	.602
Diagnosis, no. (%)			
CVID	38 (86)	35 (78)	.409
XLA	6 (14)	10 (22)	.409
Chronic pulmonary diseases, no. (%)			
COPD (all stages)	22 (50)	23 (51)	.543
Stage I	6 (14)	3 (7)	.283
Stage II	9 (20)	10 (22)	.522
Stage III-IV	7 (16)	10 (22)	.313
Bronchiectasis	36 (82)	40 (89)	.260



Janjua et al. Cochrane Database of Systematic Reviews 2021
Milito et al. JACI 2019

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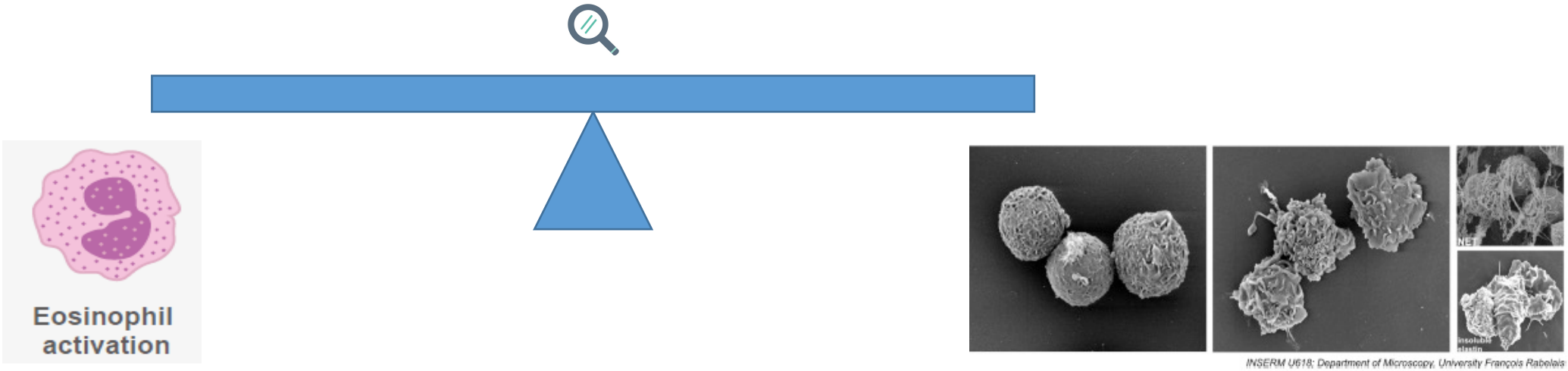
Inhalative treatment and management with concurrent bronchiectasis

1. SABA (short-acting beta agonist)
2. Saline solution (0,9% -6%)
3. Improved mucociliary clearance
4. LAMA/LABA/ICS

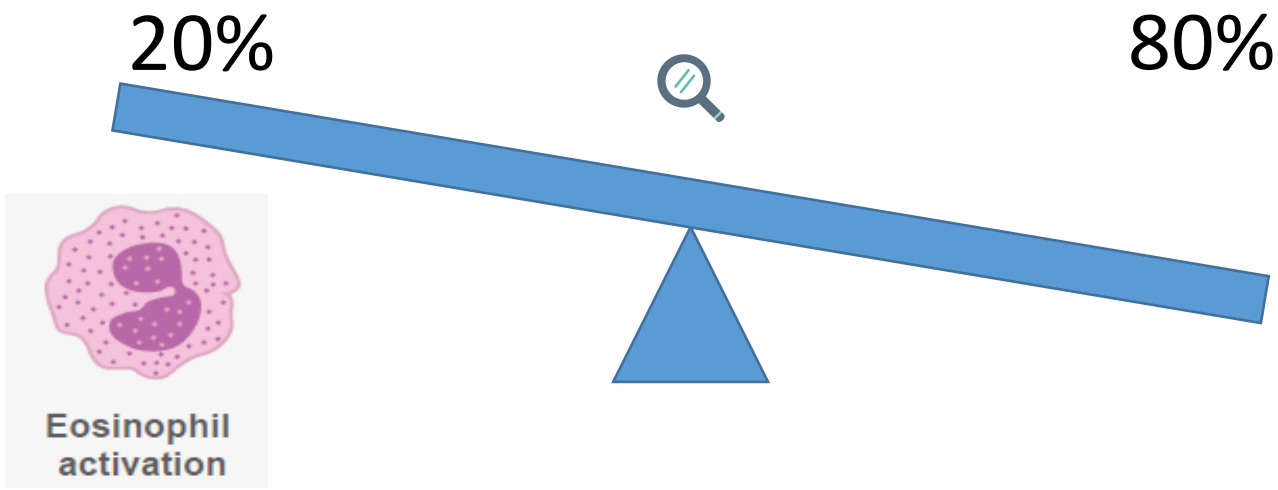
Additional elements of bronchiectasis management:

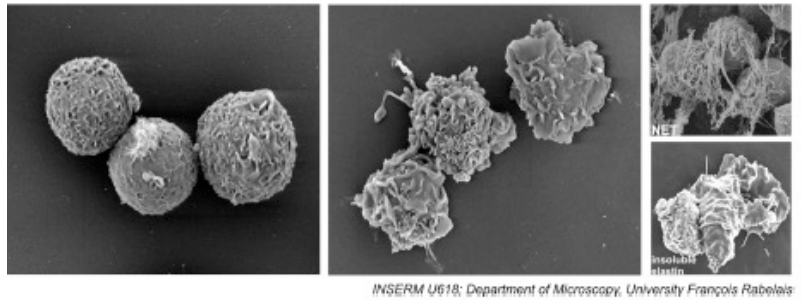
- Microbiological sputum surveillance (colonization with *Pseudomonas aerug.* or NTM?)
- Pulmonary physiotherapy, exercise and use of portable mucus clearance device
- Sufficient IgG levels
- Antimicrobial prophylaxis (macrolides, TMP/SMX) -> check cQT time (ECG) and NTM before

Neutrophilic and eosinophilic inflammation in bronchiectasis:



Neutrophilic and eosinophilic inflammation in bronchiectasis (in non-IEI patients):





INSERM U618; Department of Microscopy, University François Rabelais

Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series

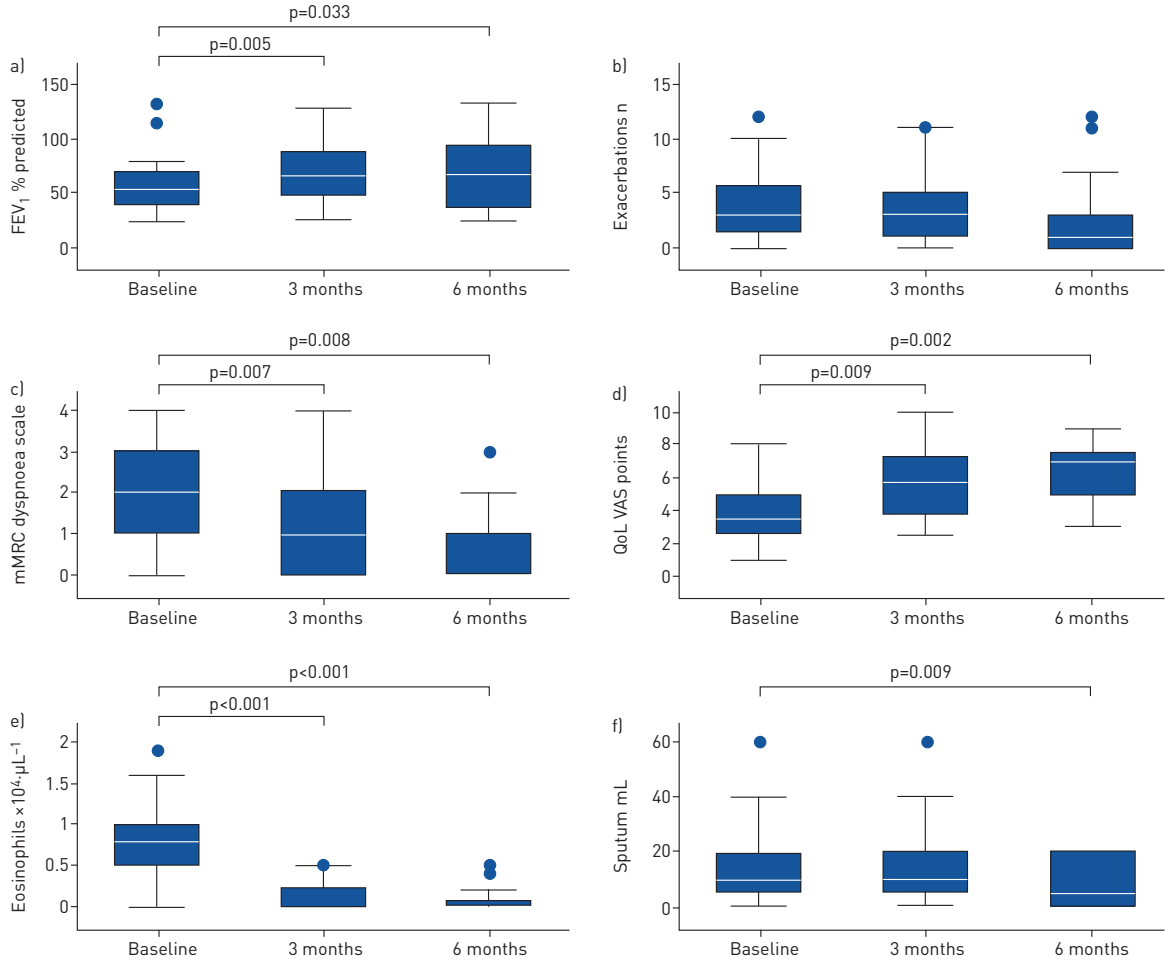


FIGURE 1 a) Forced expiratory volume in 1 s (FEV_1); b) annualised exacerbation frequency; c) modified Medical Research Council (mMRC) dyspnoea scale; d) quality of life (QoL); e) eosinophils; and f) 24-h sputum volume at baseline and after 3 and 6 months of treatment. VAS: visual analogue scale.

Eur Respir J 2020; 55: 1901333

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Role of neutrophils and neutrophil proteases:

	Azurophilic granules	Specific granules	Gelatinase granules	Secretory vesicles
Antibacterial proteins	Azurocidin Myeloperoxidase Defensins Cap 57 (bactericidal permeability-inducing protein) Lysozyme	Lipocalin 2 (NGAL) Lactoferrin hCAP18 Haptoglobin Pentraxin3 Lysozyme $Gp91^{phox}$ / $p22^{phox}$	Cathelicidin (CAP-18) Lysozyme $Gp91^{phox}$ / $p22^{phox}$	$Gp91^{phox}$ / $p22^{phox}$
Proteases	Neutrophil elastase Cathepsin G Proteinase 3 (myeloblasin)	µPA Collagenase (MMP8)	Gelatinase B (MMP9) Leukolysin (MMP25) Collagenase (MMP8)	Leukolysin (MMP25) Proteinase 3 (myeloblastin)
Adhesion molecules		Mac-1(CD11b/ CD18) CD 66 CD 67	Mac-1(CD11b/CD18) CD 67	Mac-1(CD11b/CD18) CD 67
Receptors	CD63 antigen (tetraspanin-30)	uPAR Laminin-R Thrombospondin-R	Ficolin-1	Complement R1 (CD35) FCγR (CD16) CD14 C1q-R Formylpeptide receptor (FPR1)
Granule trafficking and docking	VAMP-7 Rab5 or Rab27a	VAMP-7	VAMP-7 VAMP-2	VAMP-7 Rab3D
Other classes of functional proteins	Heparin-Binding Protein (HBP) β-Glucoronidase Granulophysin (CD63) α1-Antitrypsin α-Mannosidase N-acetyl-β-glucosaminidase Sialidase Presenilin	β2-Microglobulin Histaminase Heparanase Stomatin CRISP3	β2-Microglobulin CRISP3 Nramp1	Heparin-Binding Protein (HBP) Plasma proteins (including albumin) Alkaline phosphatase DAF CD10 CD13 Nramp1

Increasing tendency of degranulation

<u>Secondary granula:</u>
NE (neutrophil elastase)
PR3 (proteinase 3)
CG (cathepsin G)

are required for transendothelial migration and extravasation into inflammed tissue. NE, PR3 and CG are also part of NETs.

The FEBS Journal 289 (2022) 3932–3953

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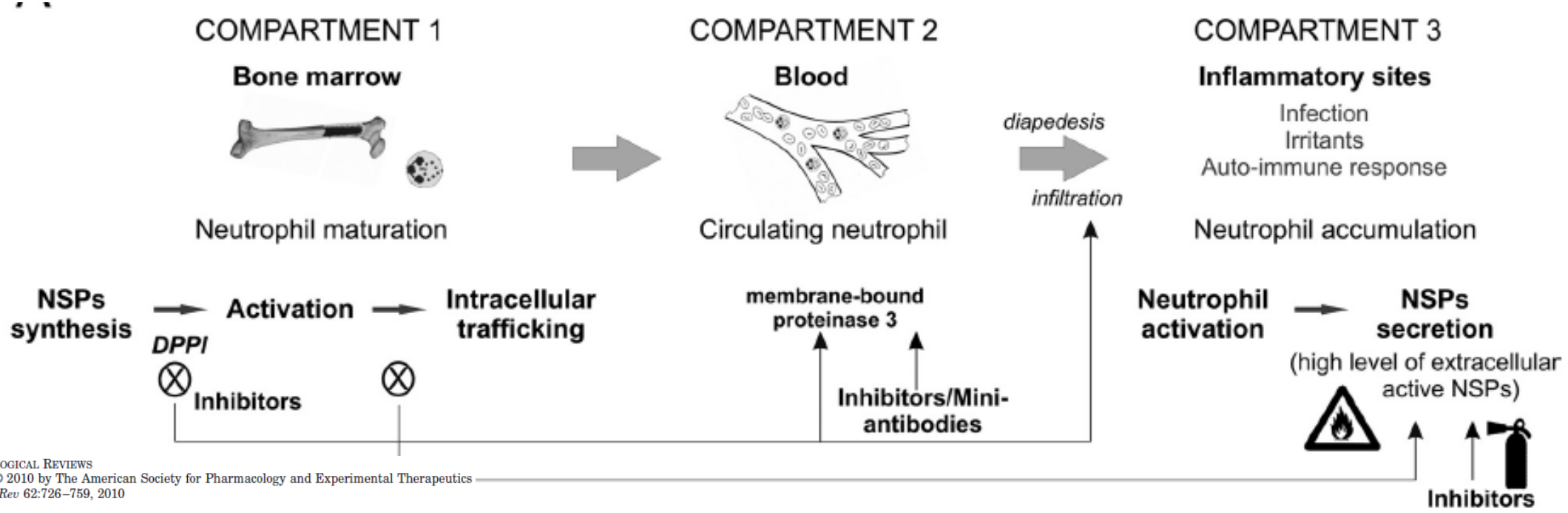
Treatment of neutrophilic inflammation:



Pharmacol Rev 62:726–759, 2010

Cathepsin C (dipeptidyl peptidase 1 - **DPP1**), is an important cysteine protease that mediates the maturation process of neutrophil serine proteases (**NSPs**) and participates in the inflammation and immune regulation process associated with polymorphonuclear neutrophils.

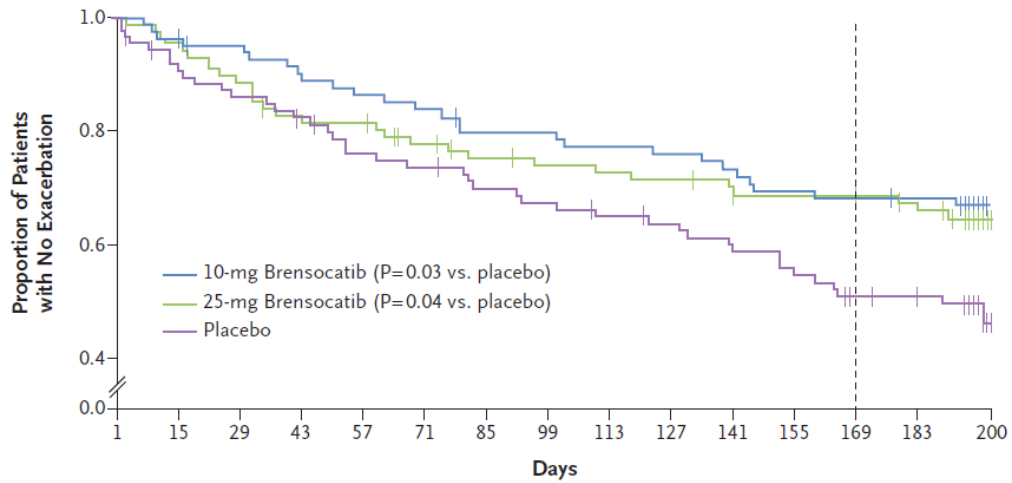
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

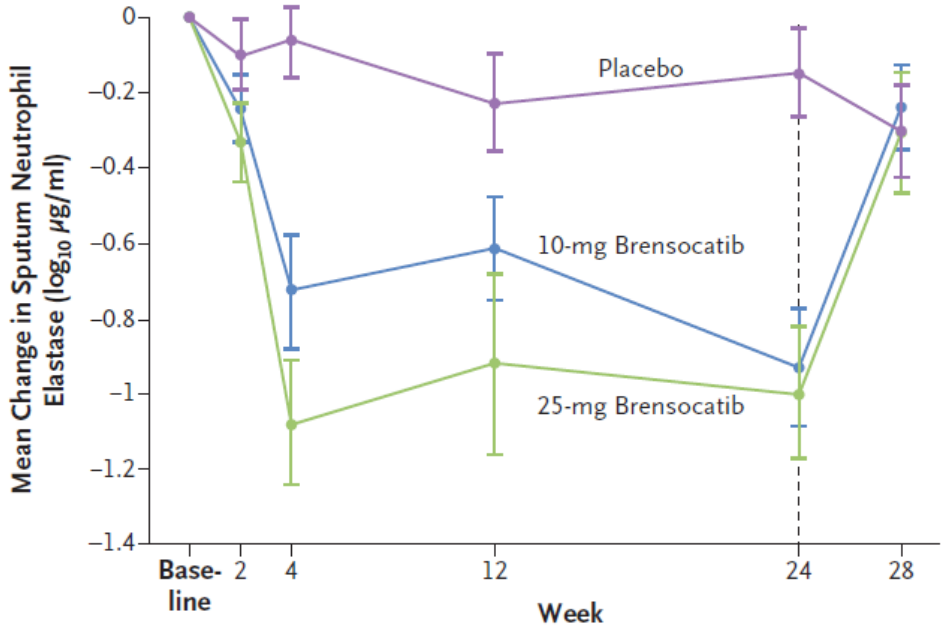
Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

James D. Chalmers, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., Mark L. Metersky, M.D., Michael R. Loebinger, B.M., B.Ch., Ph.D., Francesco Blasi, M.D., Ph.D., Oriol Sibila, M.D., Ph.D., Anne E. O'Donnell, M.D., Eugene J. Sullivan, M.D., Kevin C. Mange, M.D., M.S.C.E., Carlos Fernandez, M.D., M.P.H., Jun Zou, Ph.D., and Charles L. Daley, M.D., for the WILLOW Investigators*

A



Cumulative No. of Events/ No. at Risk															
10-mg Brensocatib	0/82	3/79	4/76	9/72	11/69	13/66	16/62	16/62	18/60	19/59	21/57	24/54	25/53	25/52	26/4
25-mg Brensocatib	0/87	4/83	10/77	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/54	26/52	26/52	28/49	29/10
Placebo	0/87	8/78	12/73	15/69	20/63	22/61	25/57	27/55	29/52	30/50	34/47	37/44	40/38	40/37	42/5



N Engl J Med 2020;383:2127-37.
DOI: 10.1056/NEJMoa2021713

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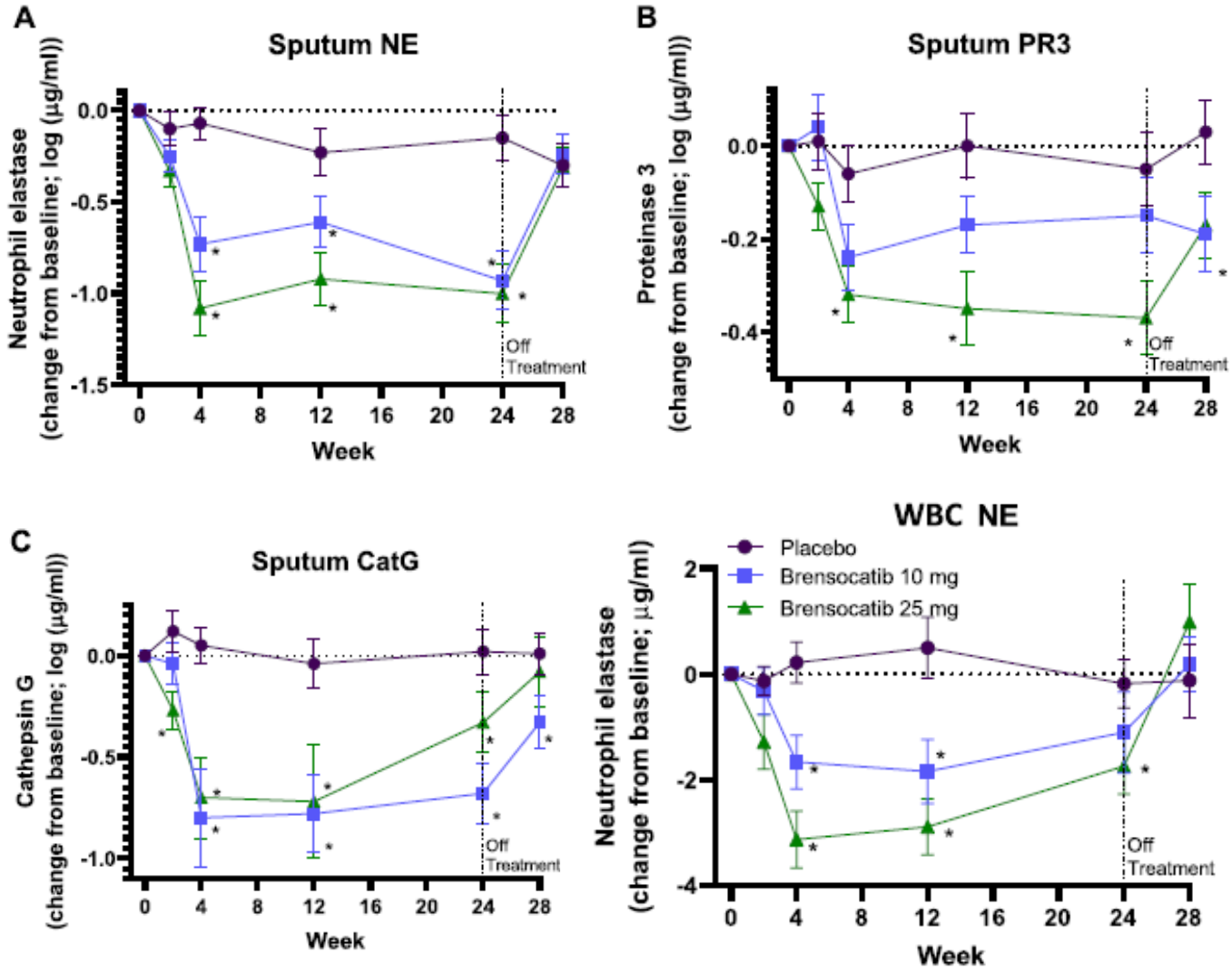
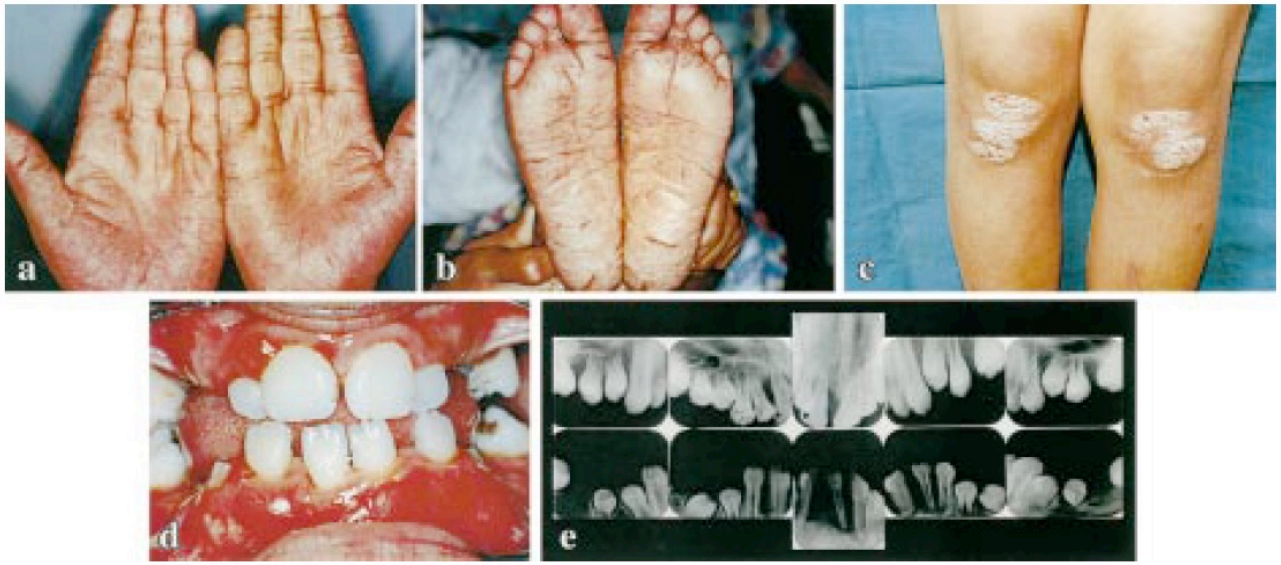


Cipolla *et al. Respiratory Research* (2023) 24:133
https://doi.org/10.1186/s12931-023-02444-z

DPP-1 Inhibition in IEI?

Mutations of the cathepsin C gene are responsible for Papillon-Lefèvre syndrome



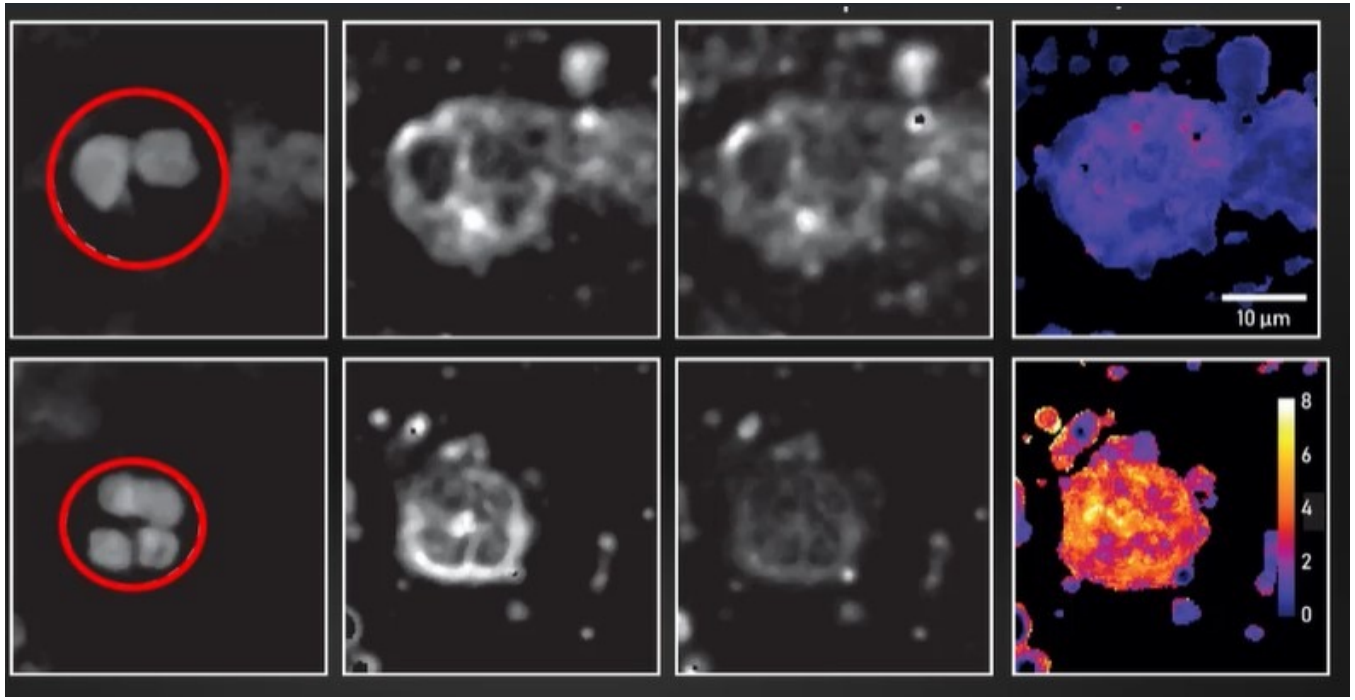
J Med Genet 1999;**36**:881–887

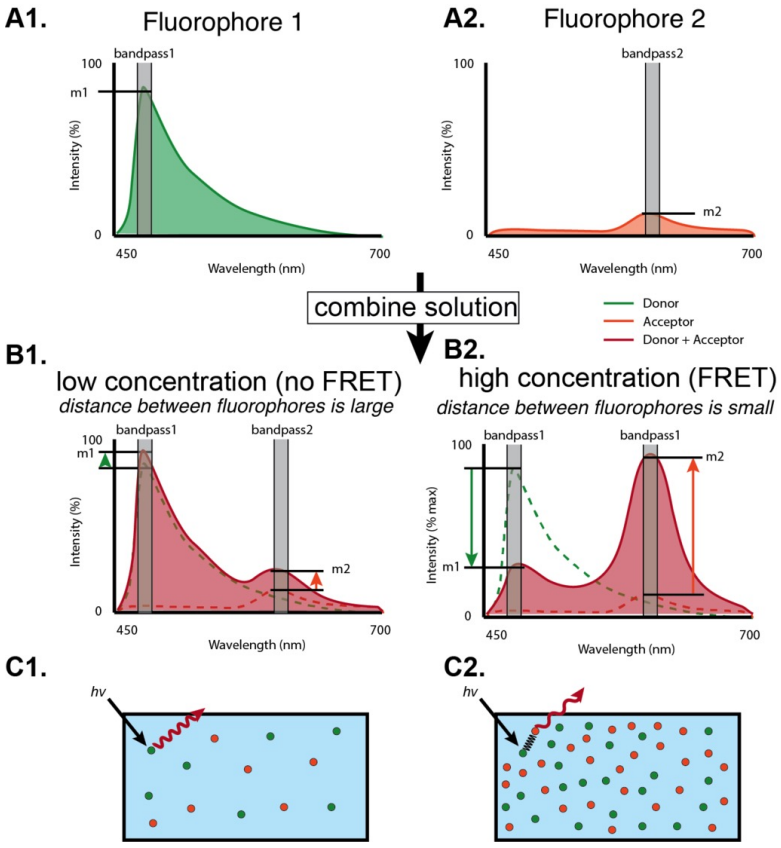
Elevated Neutrophil elastase in airways of IEI patients with bronchiectasis?

Outlook (1):

w inhibitor

w/o inhibitor





FRET: Förster resonance energy transfer

DOI: 10.3791/62193

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Asthma and COPD: localized immunodeficiencies?

Variable	Univariate analysis		
	cOR	95% CI	p value
IgA, mg/dL	0.997	0.994–1.000	0.080
IgA < 140 mg/dL	2.306	1.049–5.071	0.038
IgA ≥ 280 mg/dL	0.706	0.379–1.315	0.273
Age	0.957	0.929–0.986	0.003
Male sex	1.933	1.117–3.346	0.019
Eosinophil ≥ 450/μL	1.792	1.010–3.180	0.046
IgE ≥ 100 IU/mL	1.833	1.022–3.288	0.042

RR for moderate/severe airway hyperresponsiveness in young (<45 years) asthma patients (n: 234). Korean J Intern Med 2017;32:137-145

SPIROMETRICS study
N: 1049 COPD patients

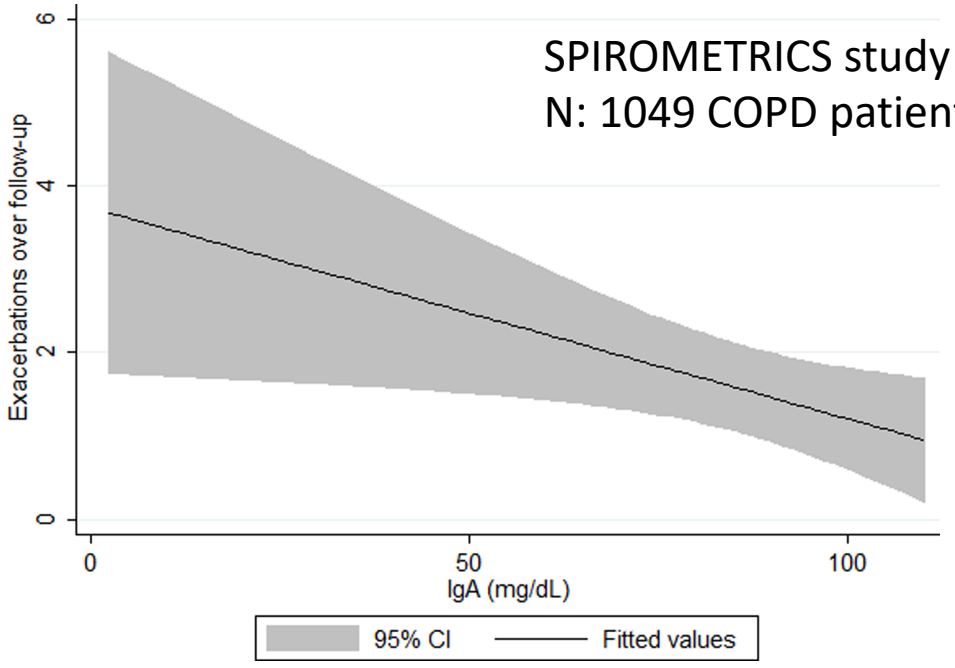


Fig 2. Unadjusted association of IgA with follow-up exacerbations among lowest decile IgA(0–120 mg/dL).

Table 2. Association of subnormal serum IgA (<70 mg/dL) with exacerbations.

	Unadjusted analysis		
	Effect size	95% CI	p-value
Dichotomous Exacerbations (Logistic regression, OR)	1.47	(0.65, 3.30)	0.353
Dichotomous severe exacerbations (Logistic regression, OR)	**3.20**	**(1.44, 7.10)**	**0.004**

Putcha N et al. 2018 PLoS ONE 13(4)

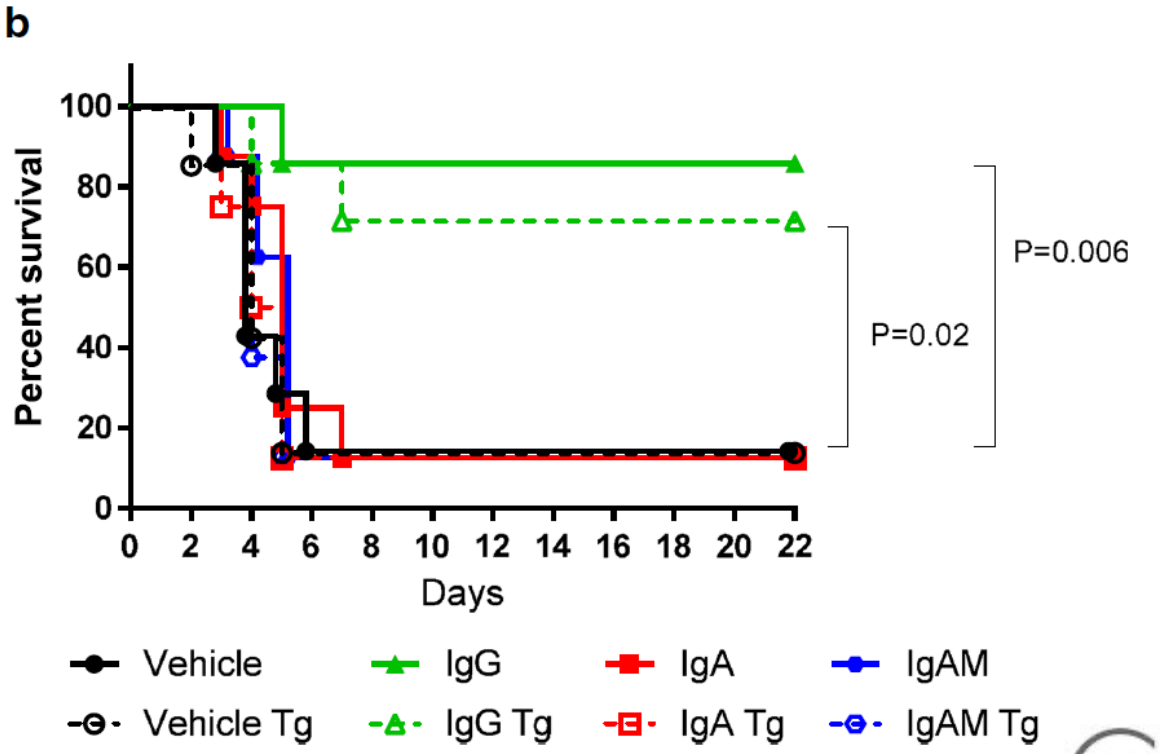
Vonarburg *et al. Respiratory Research* (2019) 20:99
https://doi.org/10.1186/s12931-019-1057-3

Respiratory Research

RESEARCH Open Access

Topical application of nebulized human IgG, IgA and IgAM in the lungs of rats and non-human primates

Cédric Vonarburg[1*], Marius Loetscher[1], Martin O. Spycher[1], Alain Kropf[1], Marlies Illi[1], Sharon Salmon[2], Sean Roberts[2], Karin Steinfuehrer[3], Ian Campbell[4], Sandra Koernig[4], Joseph Bain[5], Monika Edler[1], Ulrich Baumann[6], Sylvia Miescher[1], Dennis W. Metzger[2], Alexander Schaub[1], Fabian Käsermann[1] and Adrian W. Zuercher[1]



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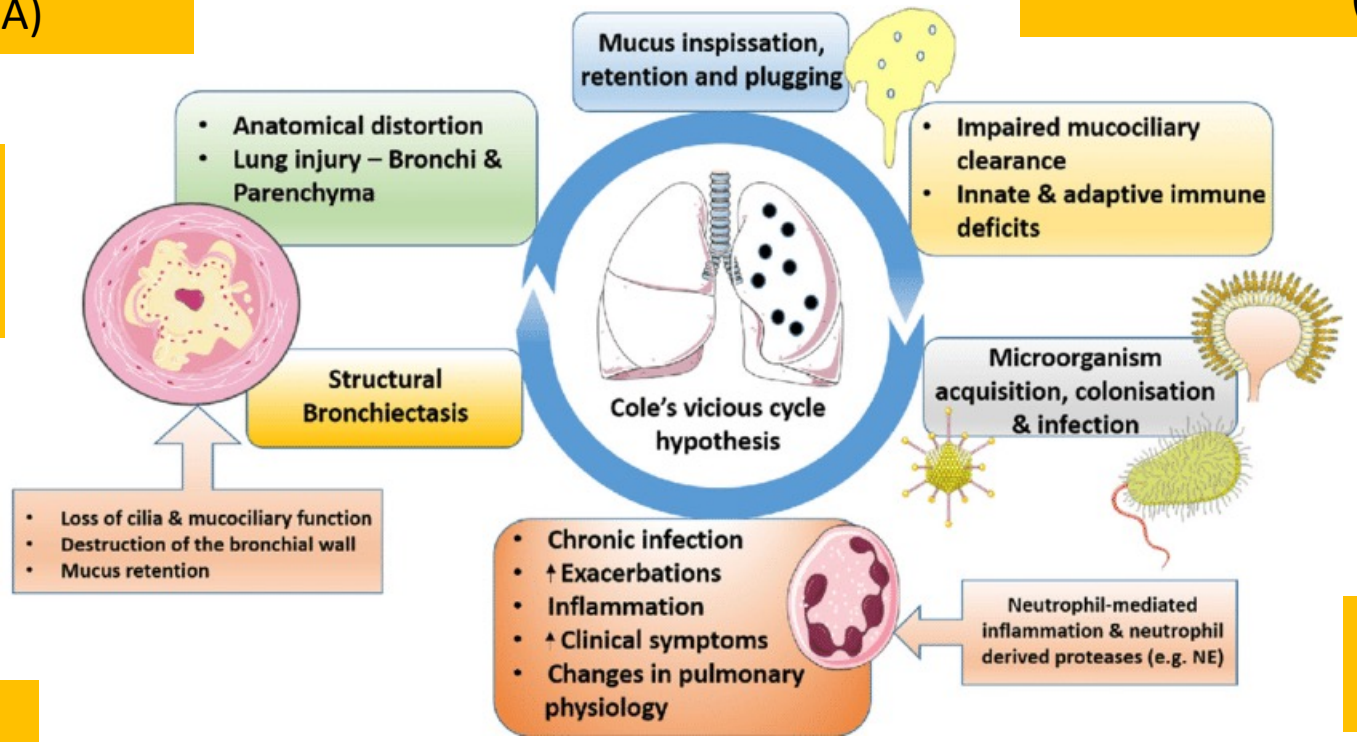
Treatment options of bronchiectasis in IEI:

Standard antiobstructive therapy (SABA/LABA/LAMA)

Localized anti-inflammatory therapy (ICS)

Systemic anti-inflammatory therapy (macrolide antibiotics)



Systemic antimicrobial prophylaxis (macrolide antibiotics)

If possible avoid systemic anti-inflammatory therapy (steroids)

Improve mucociliary clearance

IgRT
Ig inhalation?

Biologics for eosinophilic type?

DPP1-inhibition?

Avoid smoking

Chandrasekaran *et al. BMC Pulmonary Medicine* (2018) 18:83
https://doi.org/10.1186/s12890-018-0638-0

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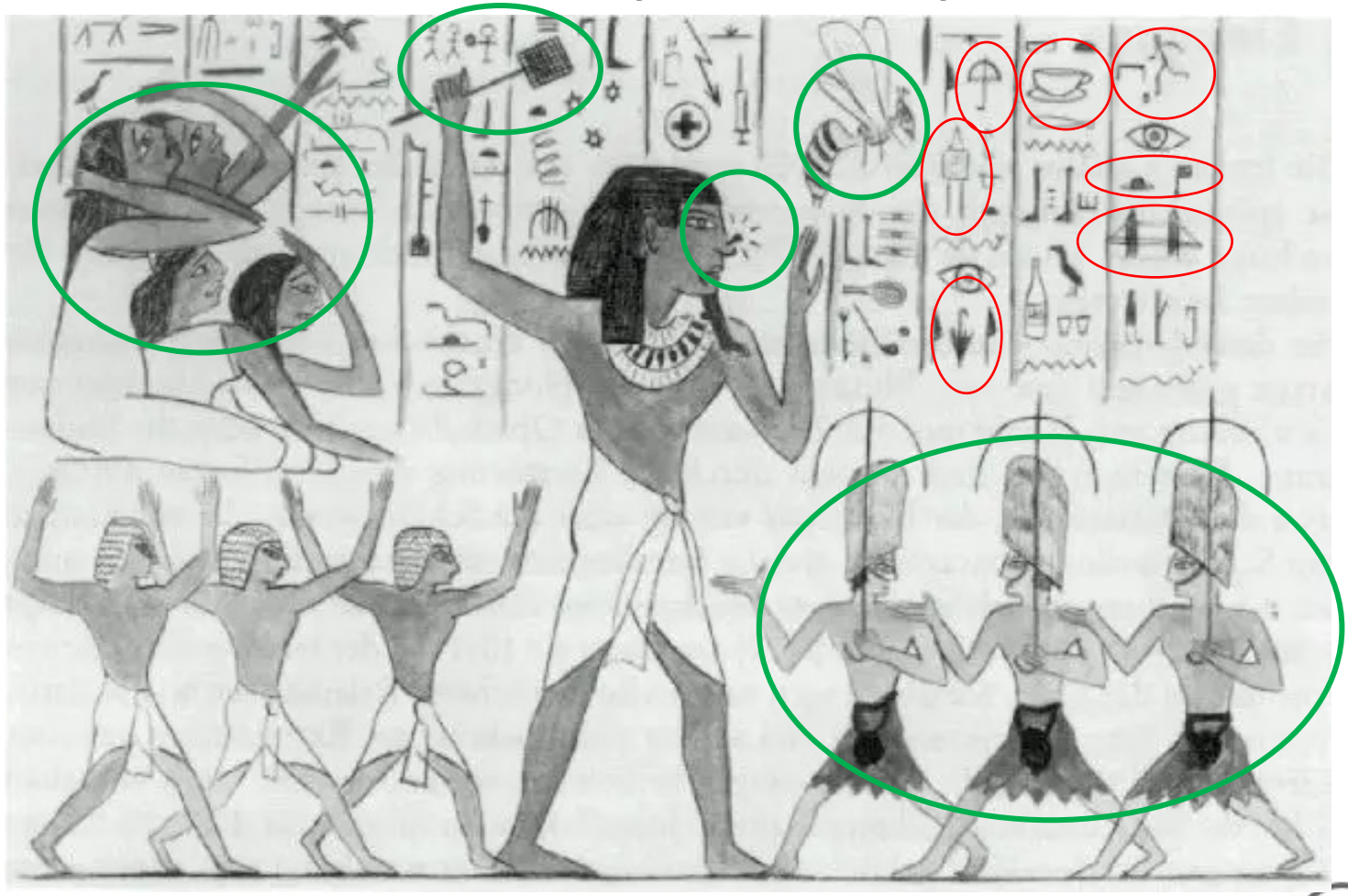
FOCiS Federation of Clinical Immunology Societies www.focisnet.org | CENTERS of EXCELLENCE

European Reference Network | rita Network Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA)

Thank you for your attention



Is this picture giving sound evidence that Pharao Menes died around 2800 BC of a wasp sting anaphylaxic shock after trying to conquer Great Britain?

leif-gunnar.hanitsch@charite.de

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