Svår astmamottagning, biologiska mm

Apostolos Bossios, lungläkare

Bitr. Överläkare, Svår astma mottagning ME Lung- och allergisjukdomar, Karolinska Universitetssjukhuset

Docent, Senior forskare, forskargruppsledare, lung- och luftväsforskning, Institutet för miljömedicin, KI

COI

- Advisory board/speaker for TEVA, AstraZeneca, GSK, Novartis, Sanofi, Chiesi.
- ERS Officer, Head of assembly 5-Airway diseases, Asthma, COP and chronic Cough
- SHARP Steering Committee
- Nordic Severe Asthma Network co-chair
- Luftvägsregistrets styrgrupp medlem

Varför ska vi behöver vi en svår astmamottagning?

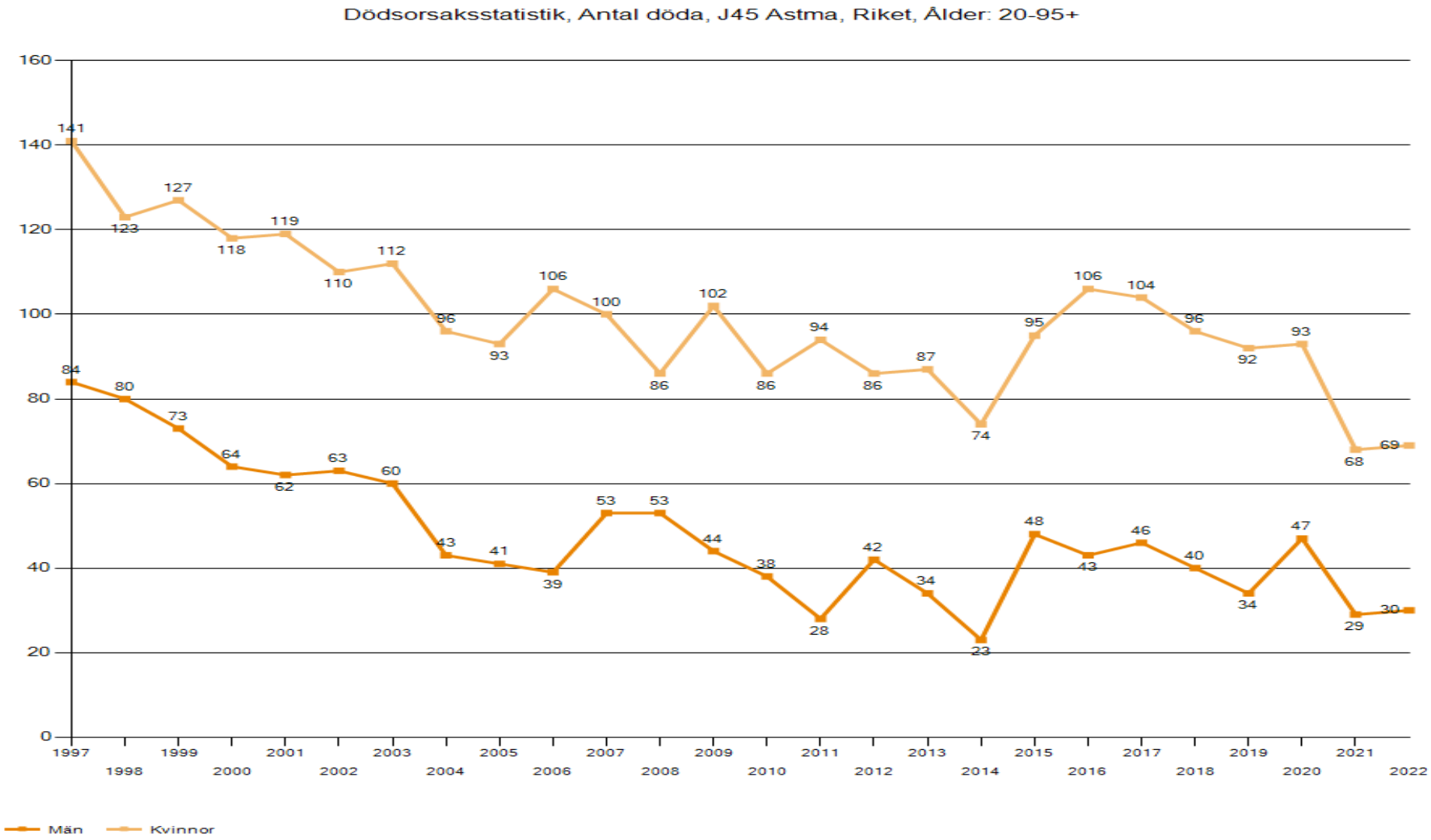
Är astma en alvarligt problem?

Astma kan bli dödsorsak

Charlotte Coleman, a star in Four Weddings and a Funeral, who died at 33 of an asthma attack at her flat In Holloway, London

The observer 2011

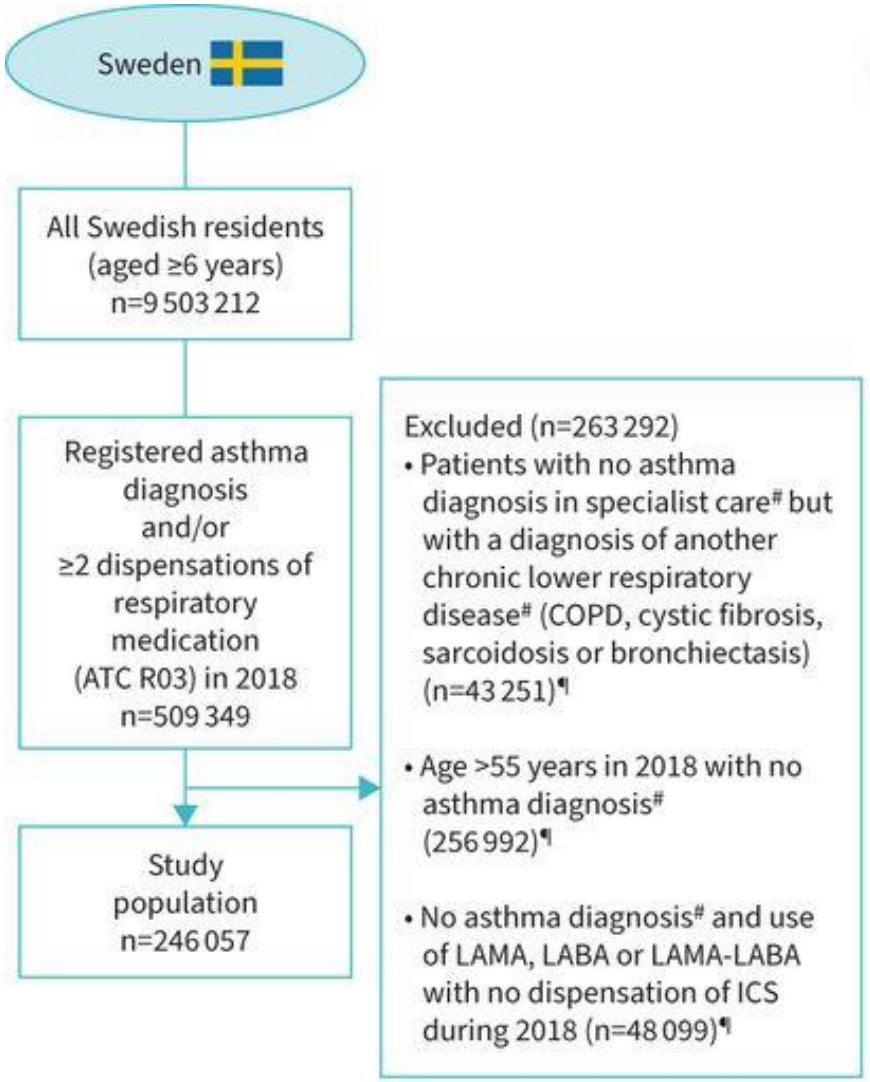
Astma som dödsorsak i Sverige

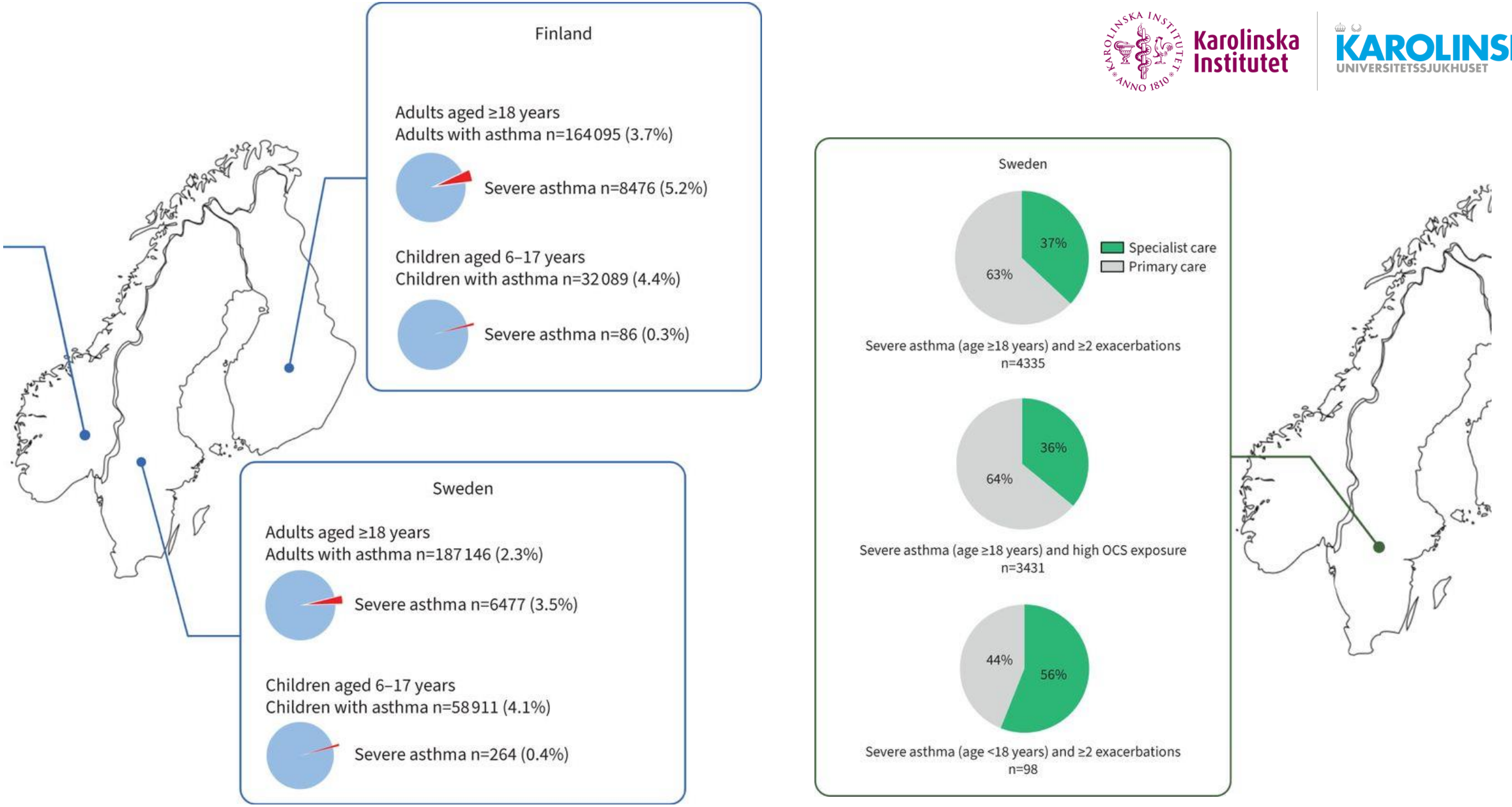


Är astma en stor problem?

Prevalence and management of severe asthma in the Nordic countries: findings from the NORDSTAR cohort

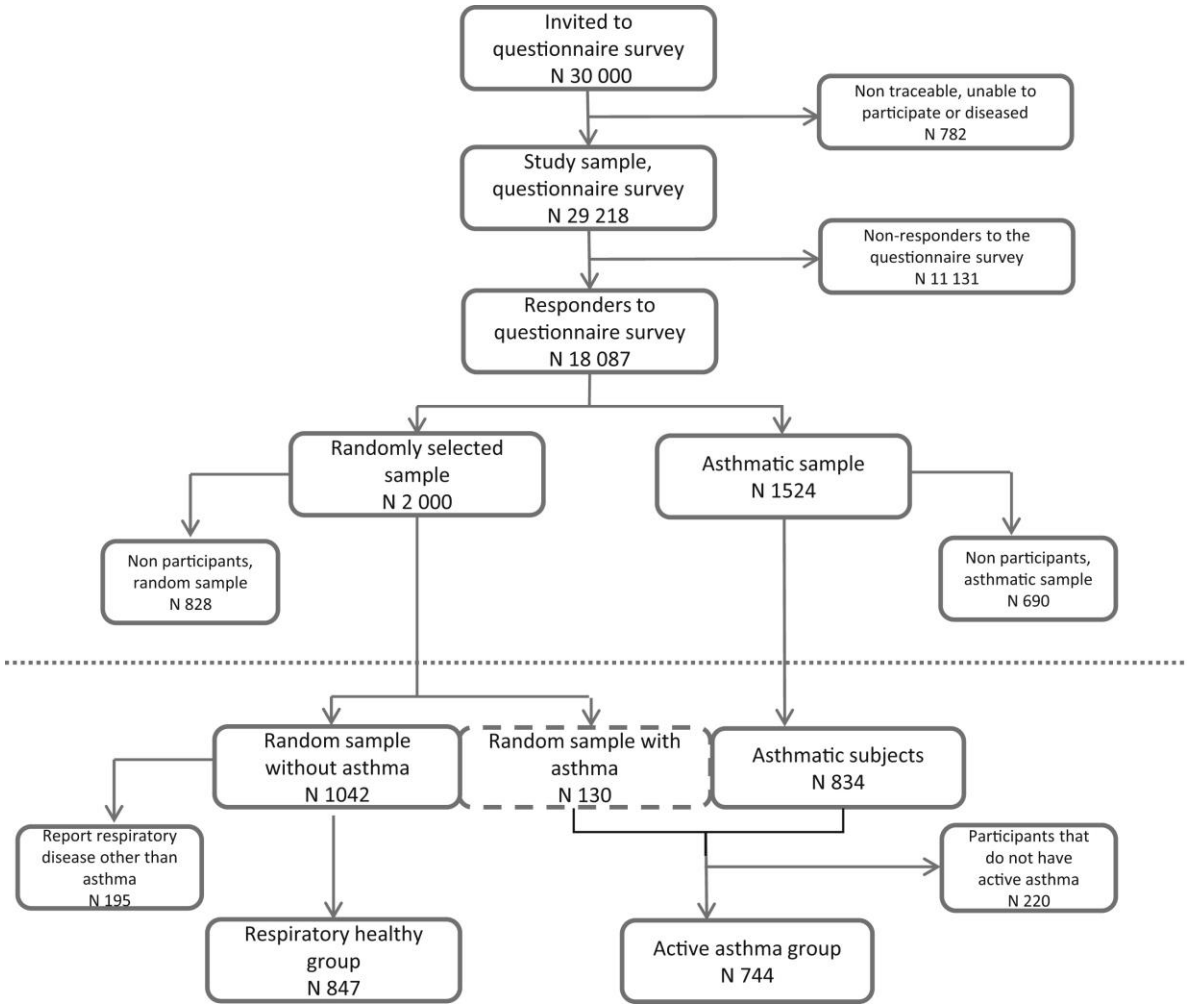
Susanne Hansen[1,2,29], Anna von Bülow[1,29], Patrik Sandin[3], Olivia Ernstsson[3,4], Christer Janson[5], Lauri Lehtimäki[6,7], Hannu Kankaanranta[7,8,9], Charlotte Ulrik[10], Bernt Bøgvald Aarli[11,12], Hanna Fues Wahl[3], Kirk Geale[3,13], Sheila Tuyet Tang[14], Maija Wolf[15], Tom Larsen[16], Alan Altraja[17,18], Helena Backman[19], Maritta Kilpeläinen[20,21], Arja Viinanen[20,21], Dora Ludviksdottir[22], Paula Kauppi[23], Asger Sverrild[1], Sverre Lehmann[11,12], Vibeke Backer[24], Valentyna Yasinska[25,26], Tina Skjold[27], Jussi Karjalainen[6,7], Apostolos Bossios[25,26,28] and Celeste Porsbjerg[1]

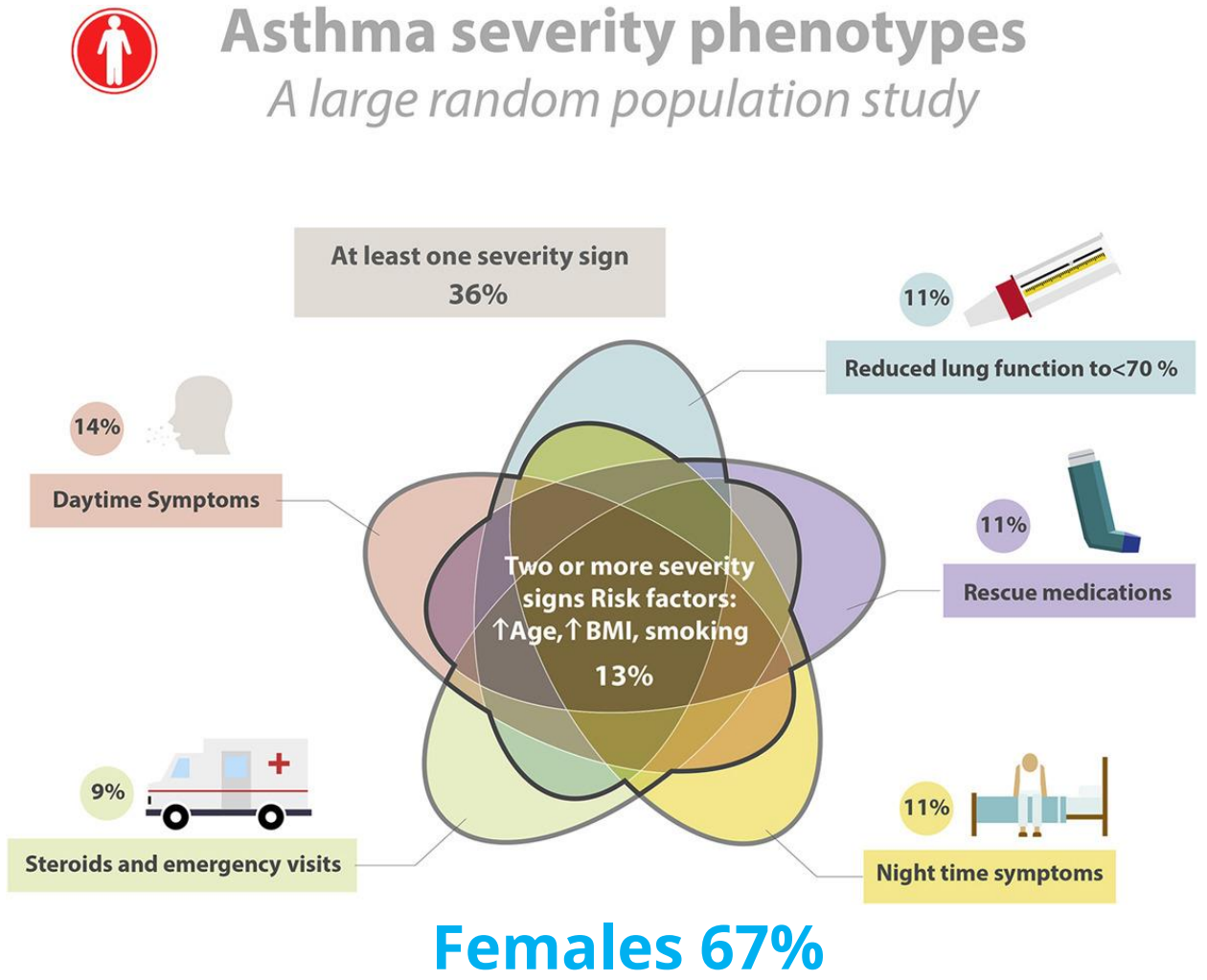




Hanssen et al ERJ OR 2022

Okontrollerade astma finns i samhälle





Females 67%

Mincheva R…Bossios A et al JACI 2017

Svår/okontrollerat astma?

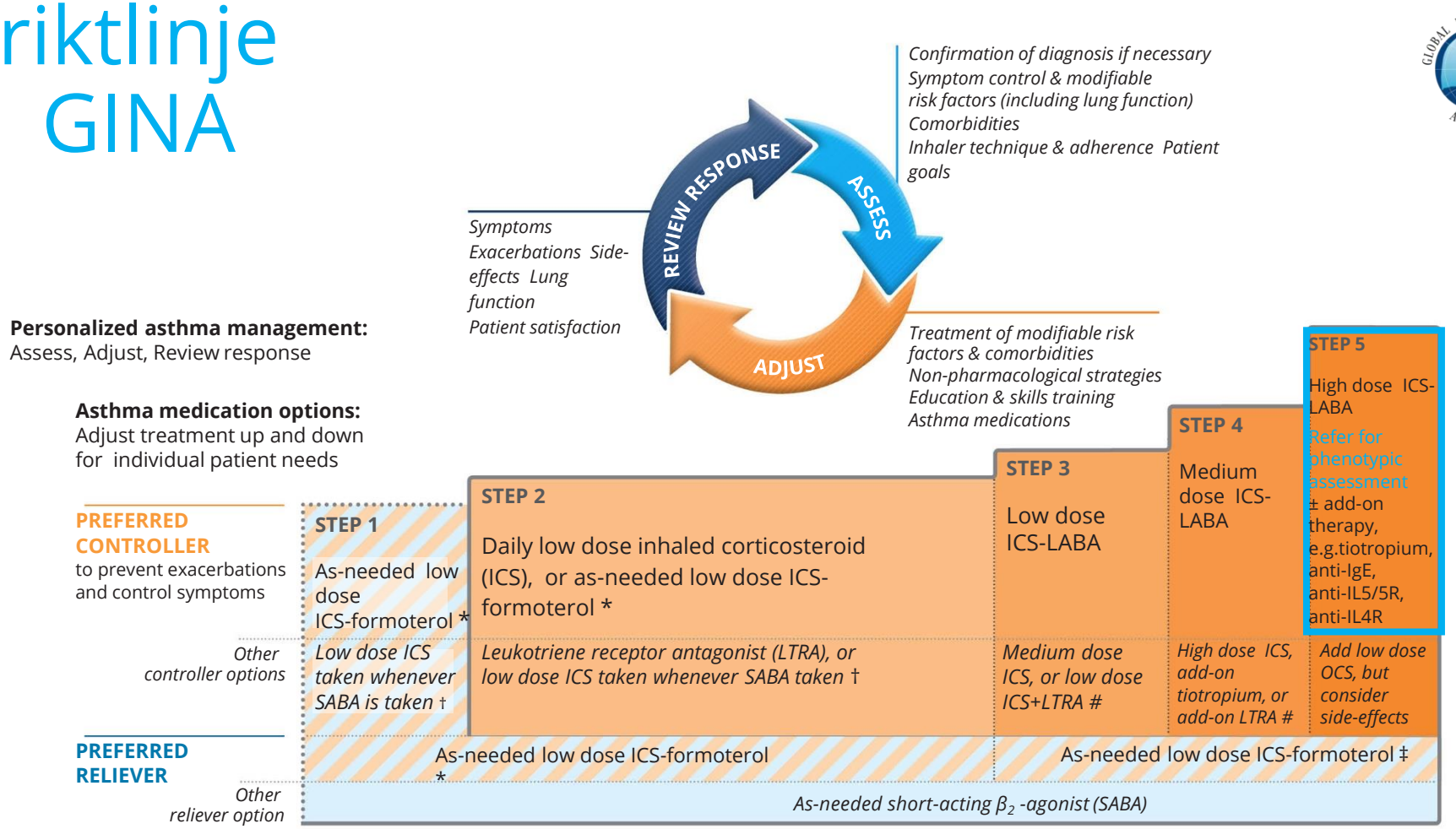
Definition av svår astma enligt ERS/ATS guidelines

Astma som kräver kontinuerlig hög medicineringsnivå, steg 4-5 enligt LMV eller GINA, under föregående år eller kortikosteroider po ≥50% av föregående år för att hållas under kontroll, (svår behandlad astma) eller som inte kan kontrolleras trots hög medicineringsnivå

Chung K ERJ 2014

Astma behandling riktlinje GINA

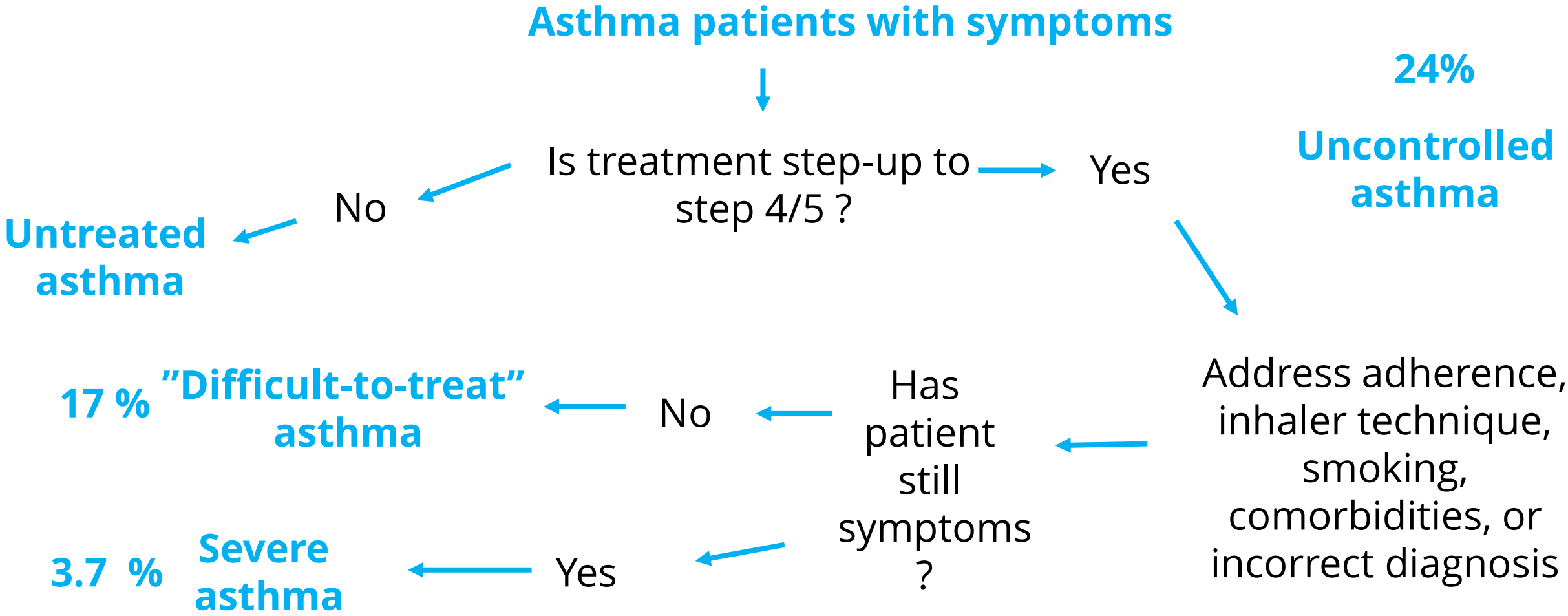
Box 3-5A
Adults & adolescents 12+ years



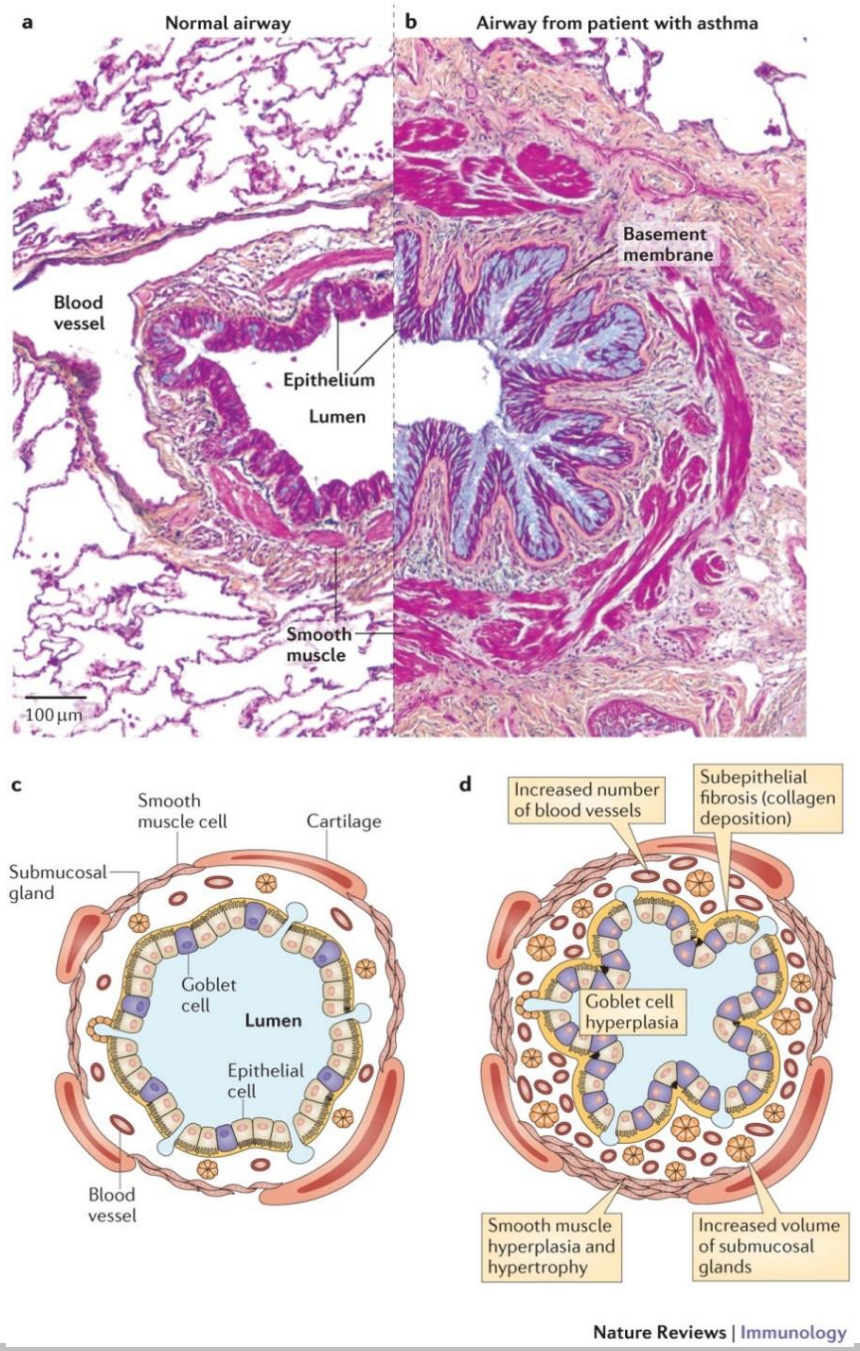
* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

Uncontrolled/Difficult-to-treat/ Severe asthma



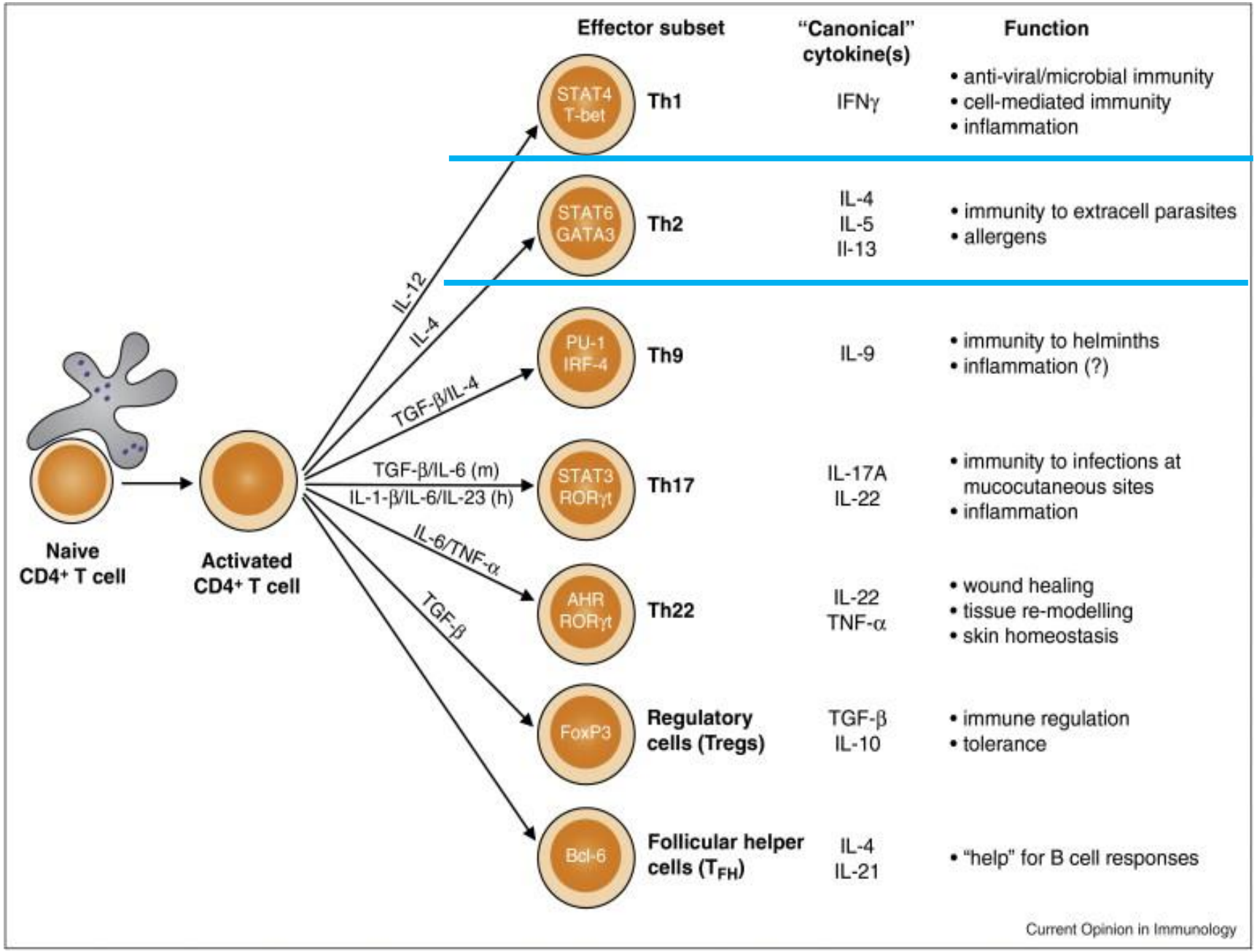
Varför?
Back to the future



Astma kronisk inflammation

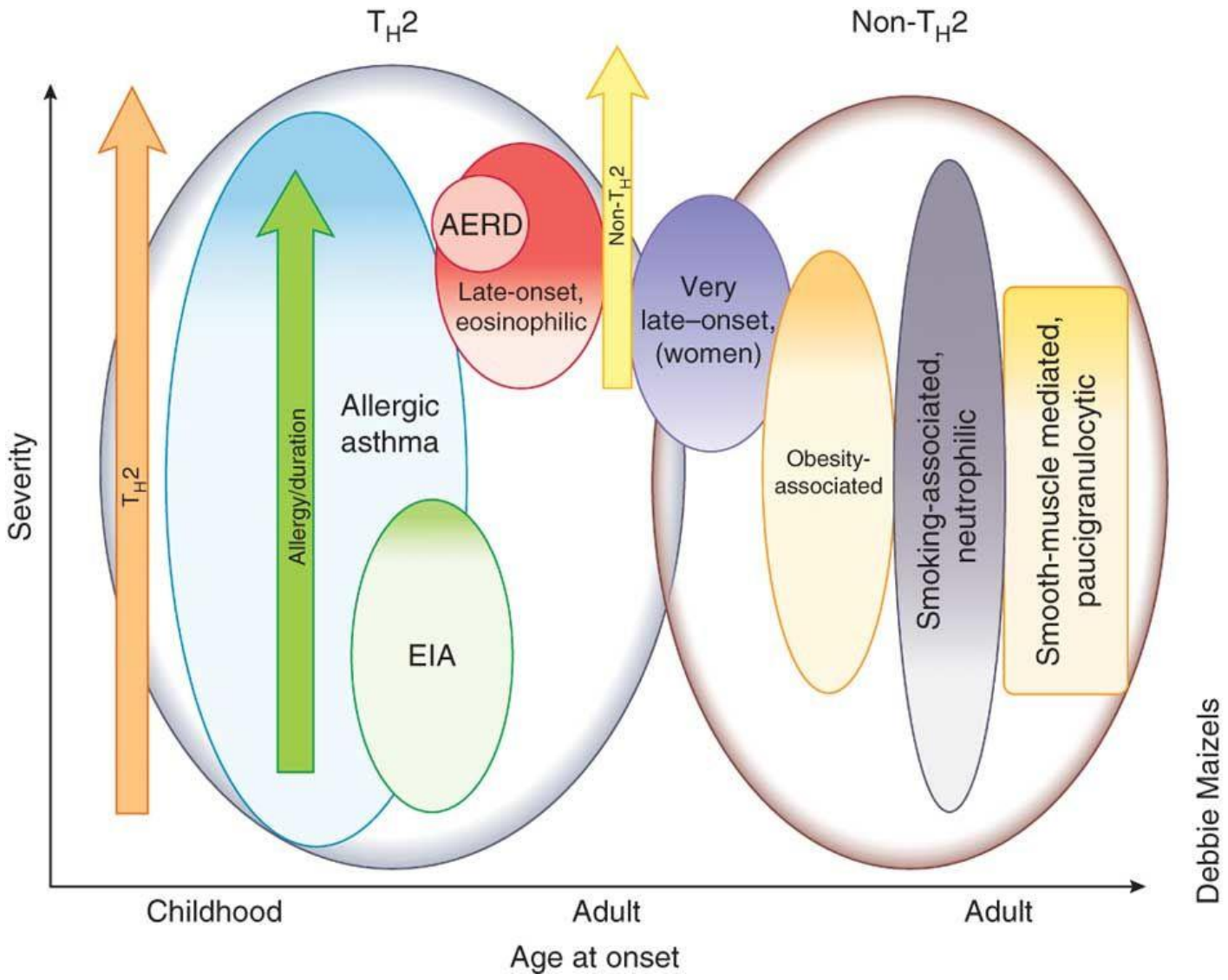
Fahy J 2015

T helper cells



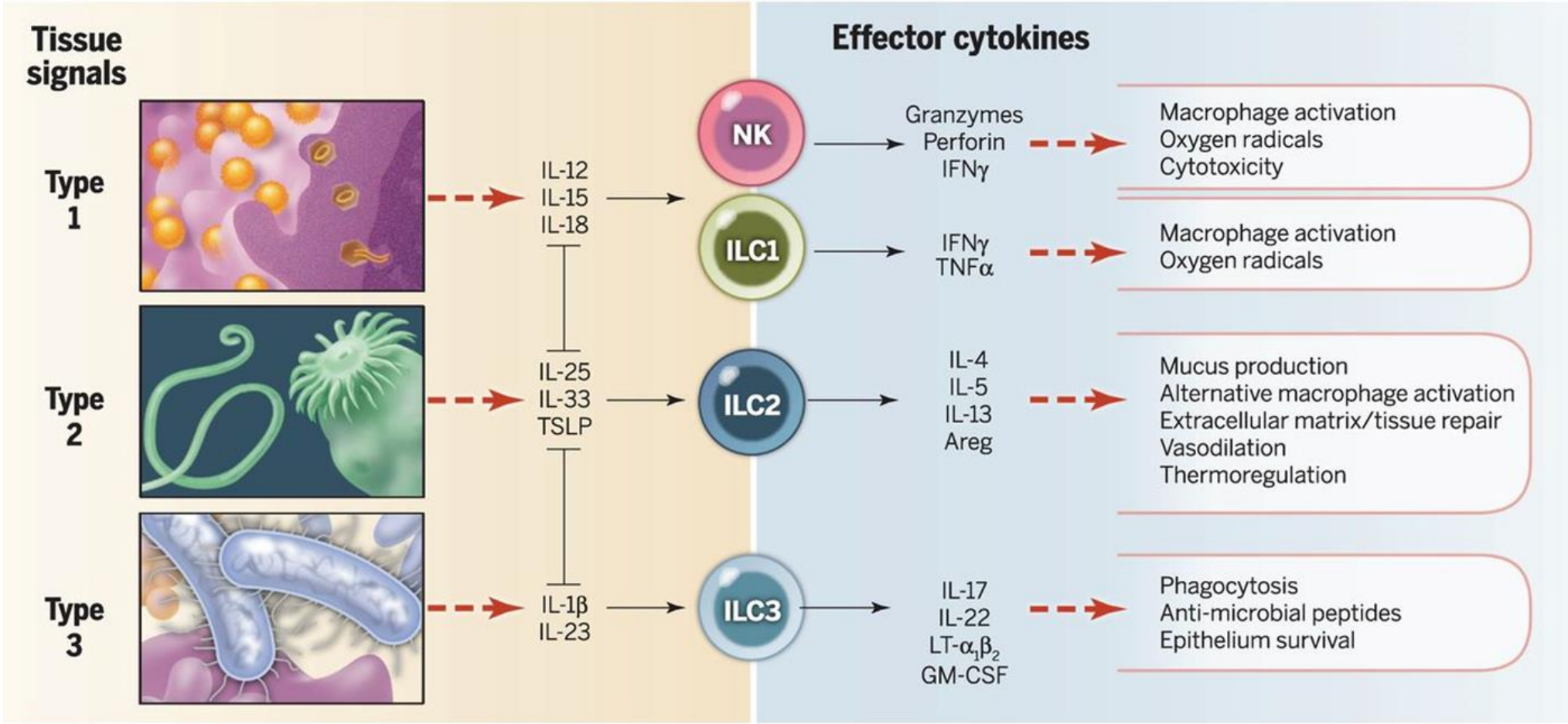
Deenick E 2011

Astma fenotyper -”traditionell”

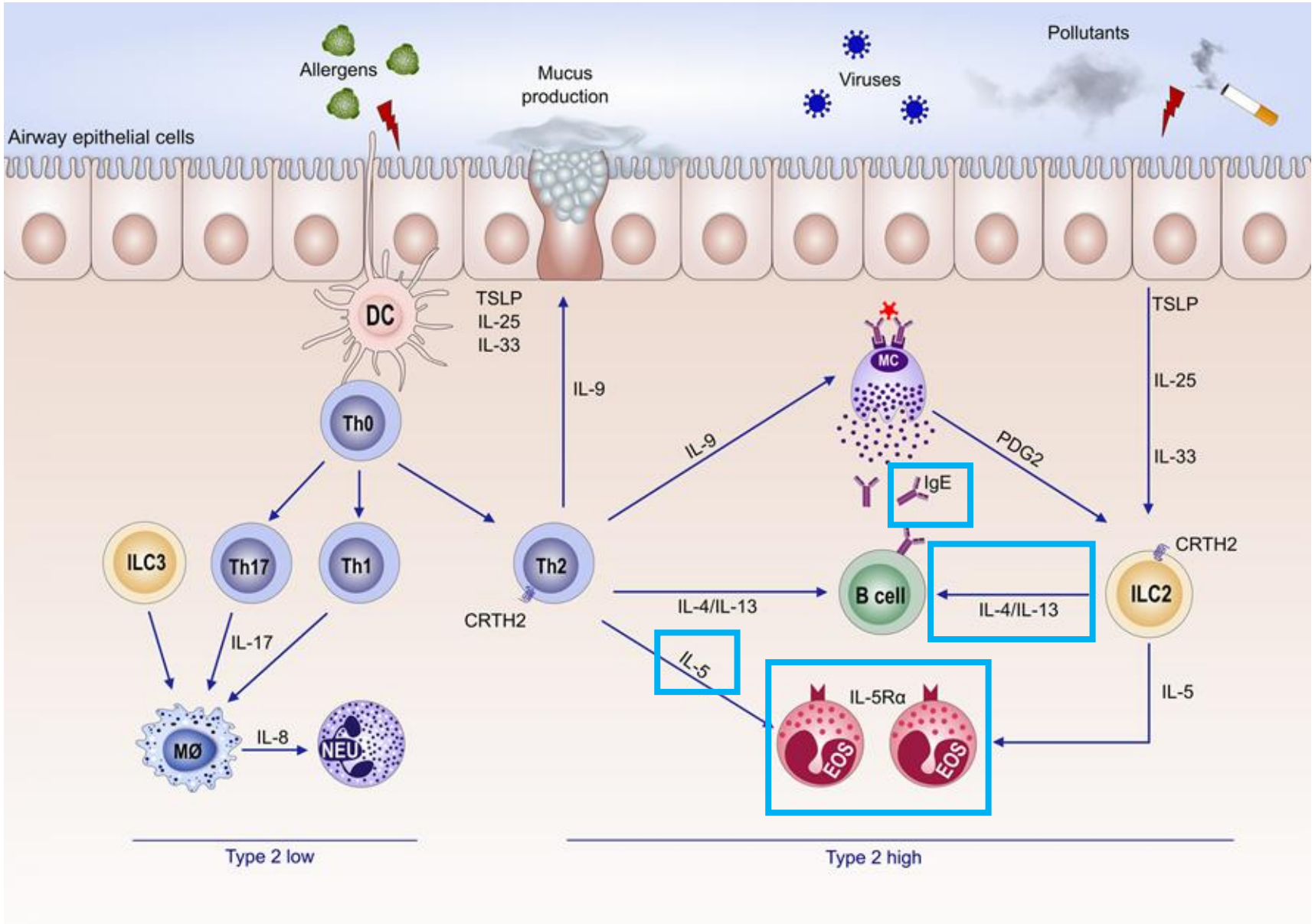


Wenzel SE Nature Med 2012

Innate Lymphoid Cells - ILCs



Eberl G Science 2015



Astma inflammation baserat fenotyper

Type-2 (T2)high & Type-2 (T2) low

Eyerich S,..., Bossios A et al Allergy 2020

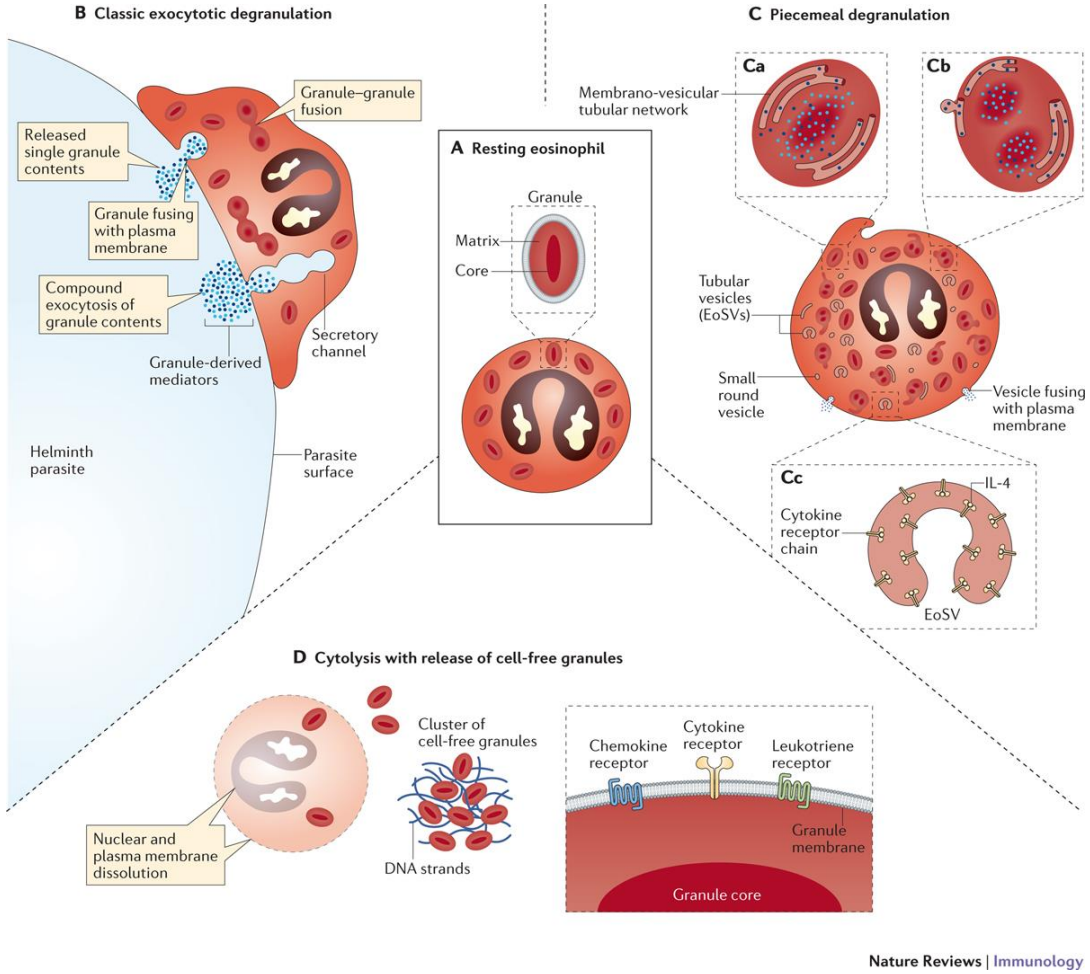
Eosinophil specific granule proteins & their secretion

- Major Basic Protein **(MBP-1 & 2):** inactivates heparin and promotes histamine release from basophils and mast cells.

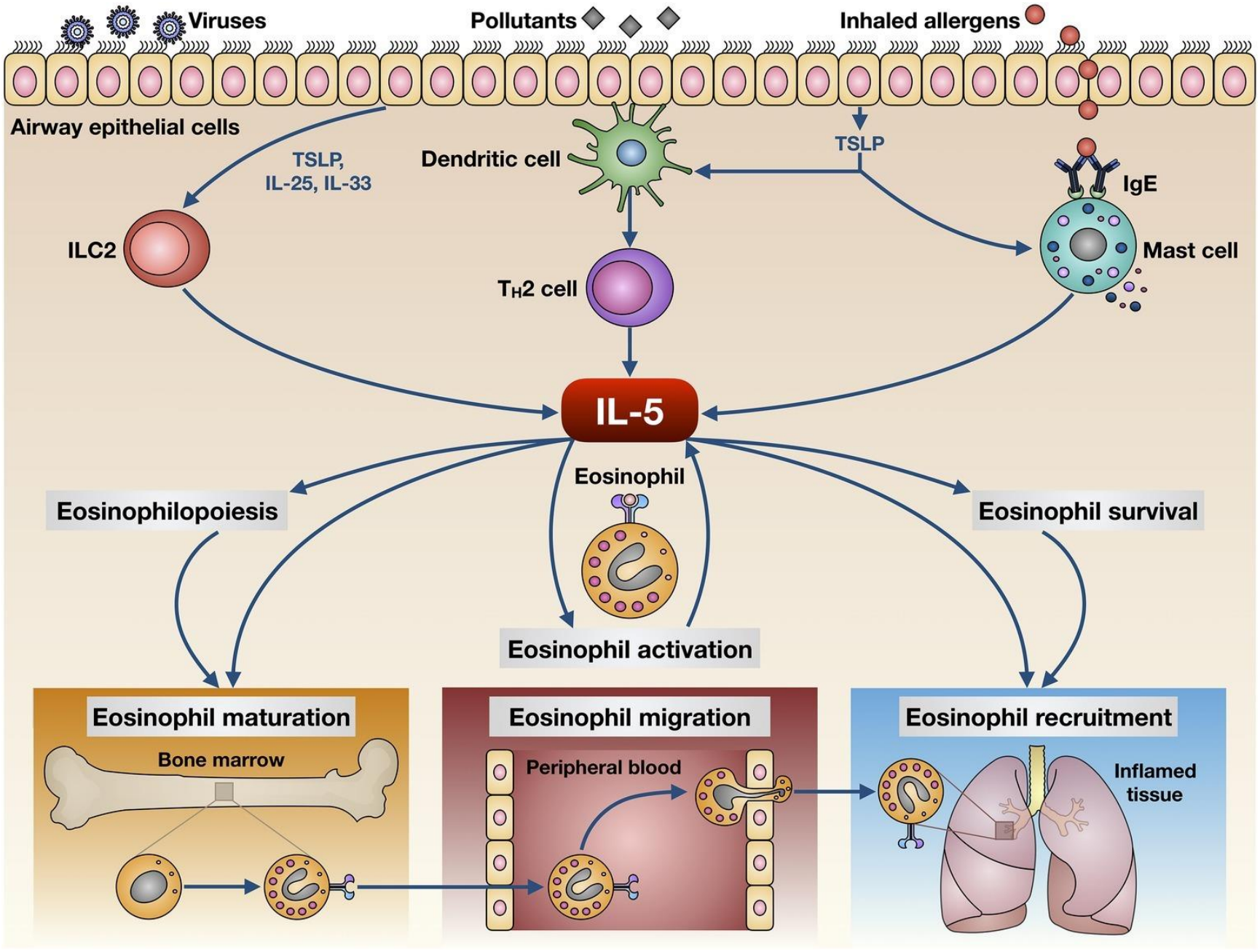
RNase Family

- Eosinophilic cationic protein **(ECP)** & Eosinophilic Neurotoxin **(EDN):** Toxicity, bactericidal properties, promotion of mast cells degranulation, destruction of tracheal epithelium

- Eosinophil Peroxidase **(EPO)** : toxic for mammalian cells, cytotoxicity towards airway epithelium



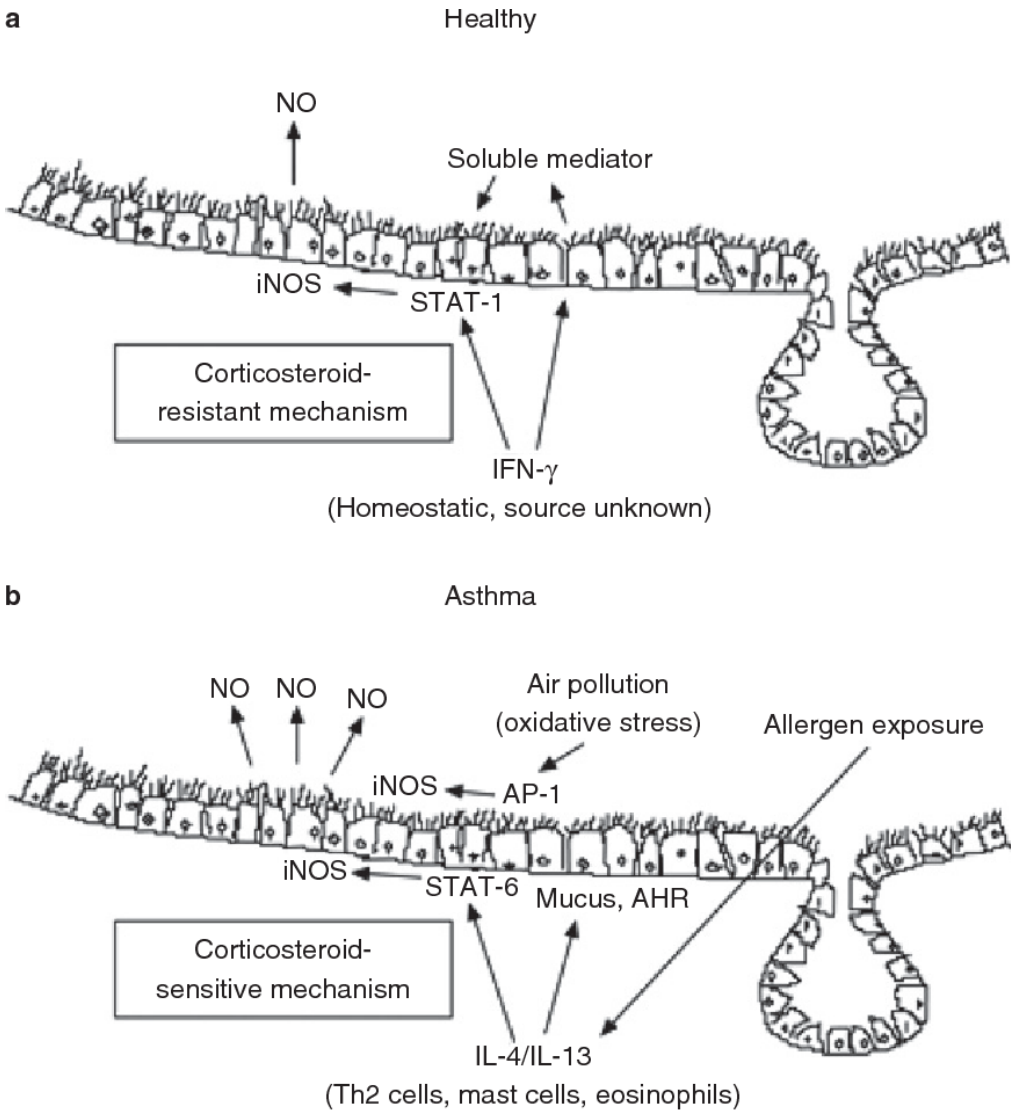
Weller P.F & Spencer LA Nature rev. Immunology 2017



IL-5 är « allt » för eosinofiler

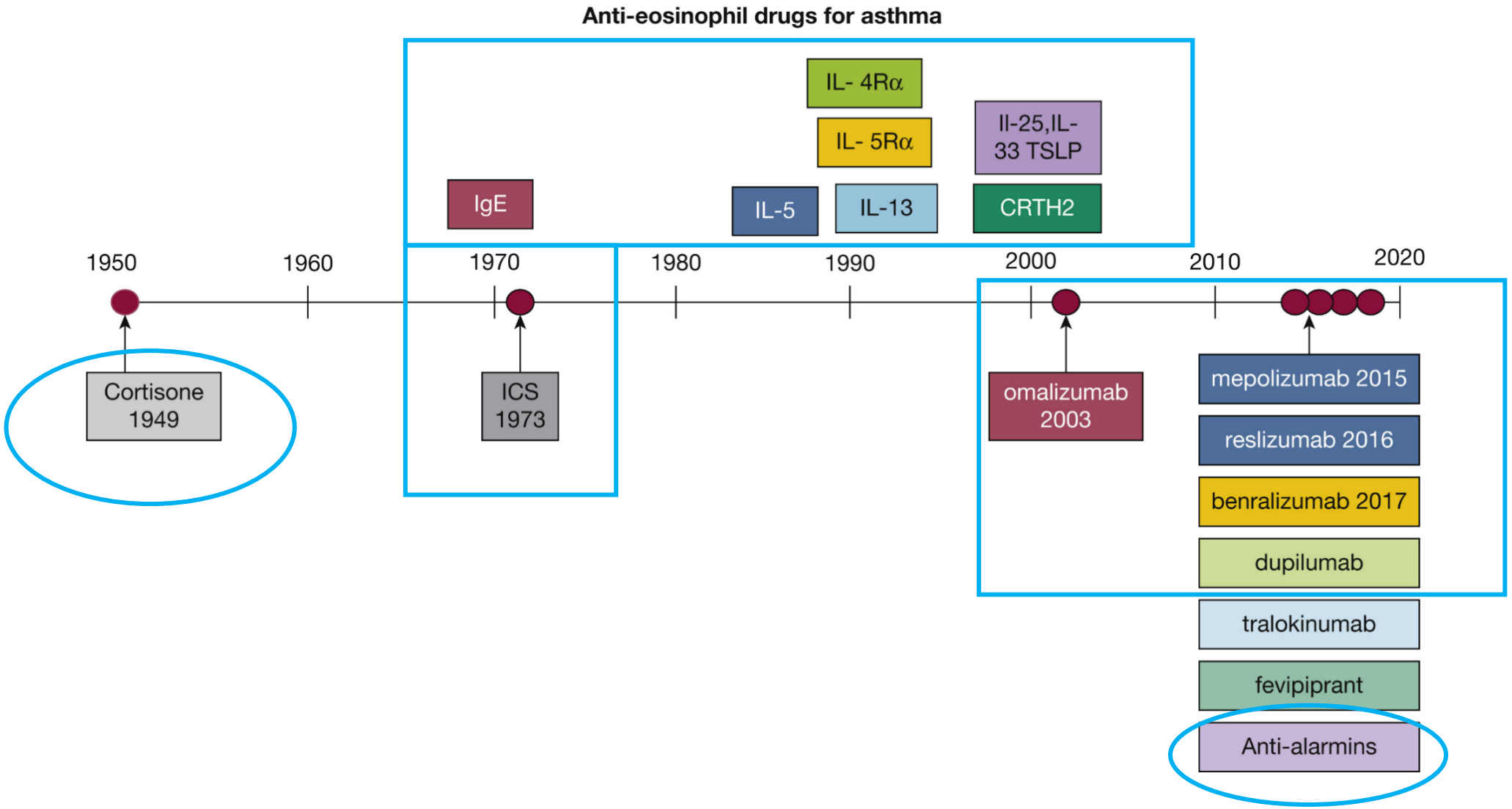
Pelaia et al. Front. Physiol 2019

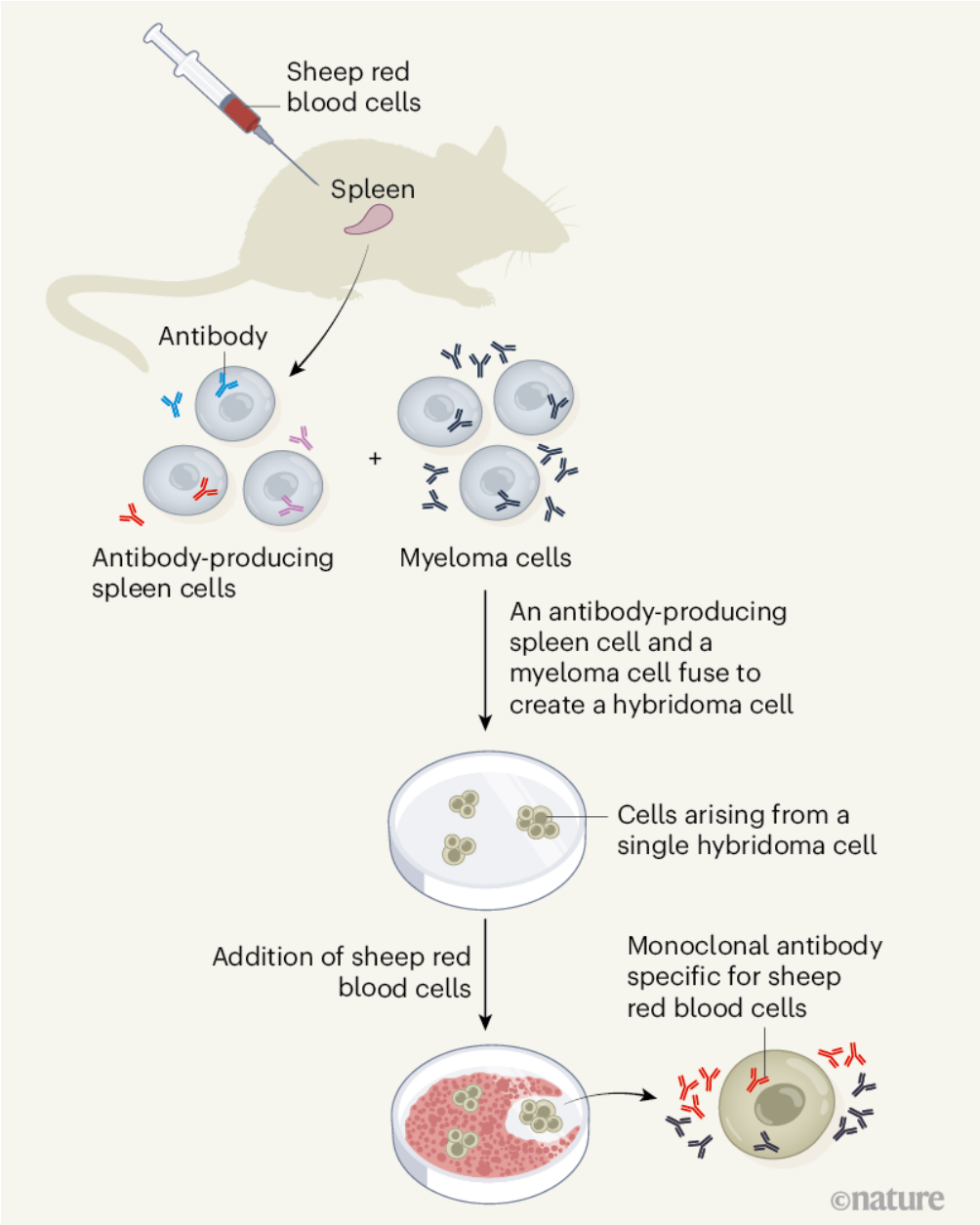
FeNo



LOW	INTERMEDIATE	HIGH
	Eosinophilic inflammation	
Unlikely	Present, but mild	Significant
<25 ppb (Children <20 ppb)	25-50 ppb (Children 20-35 ppb)	>50 ppb (Children >35 ppb)
Responsiveness to corticosteroids are less likely	Should be interpreted cautiously and with reference to the clinical context	Responsiveness to corticosteroids are likely in symptomatic patients

Behandla astma inflammation

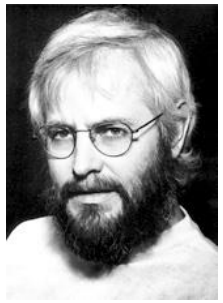




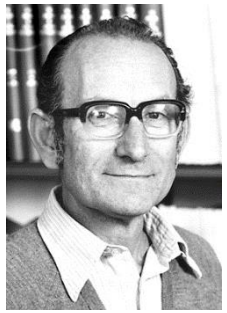
Monoklonala antikroppar

Antibodies produced from a single clone of B cells against a single epitope

The Nobel Prize in Physiology or Medicine 1984



Georges J.F. Köhler



César Milstein

Niels K. Jerne

Köhler, G. & Milstein, C. *Nature* **256**, 495–497 (1975)

Biologisk behandling definition

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

REVIEW ARTICLE

EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders

O. Boyman[1], C. Kaegi[1], M. Akdis[2,3], S. Bavbek[4], A. Bossios[5], A. Chatzipetrou[6], T. Eiwegger[7], D. Firinu[8], T. Harr[9], E. Knol[10], A. Matucci[11], O. Palomares[12], C. Schmidt-Weber[13], H.-U. Simon[14], U. C. Steiner[15], A. Vultaggio[11], C. A. Akdis[2,3] & F. Spertini[16]

Biologic agents (also termed biologicals or biologics) are therapeutics that are synthesized by living organisms and directed against a specific determinant, for example, a cytokine or receptor.

Biologisk för astma (Sverige-Europa)

- **Omalizumab (Anti-IgE):**, Allergisk astma, Kronisk rinosinuit med näspolyper(CRSwNP), Kronisk spontan urtikaria .
- **Mepolizumab (Anti-IL5)**: Svår eosinofil astma, Kronisk rinosinuit med näspolyper, Eosinofil granulomatös polyangit (EGPA) , Hypereosinofilt syndrom (HES)
- **Reslizumab (Anti-IL5)**: Svår eosinofil astma
- **Benralizumab (Anti-IL5Ra):** Svår eosinofil astma
- **Dupilumab (Anti-IL4Ra):** Svår astma med typ 2 inflammation, Kronisk rinosinuit med näspolyper, Chronic Rinosinusit with nasal polyps, måttlig till svår atopisk dermatit
- **Tezepelumab (Anti-TSLP) :** Svår astma

Anti-IgE

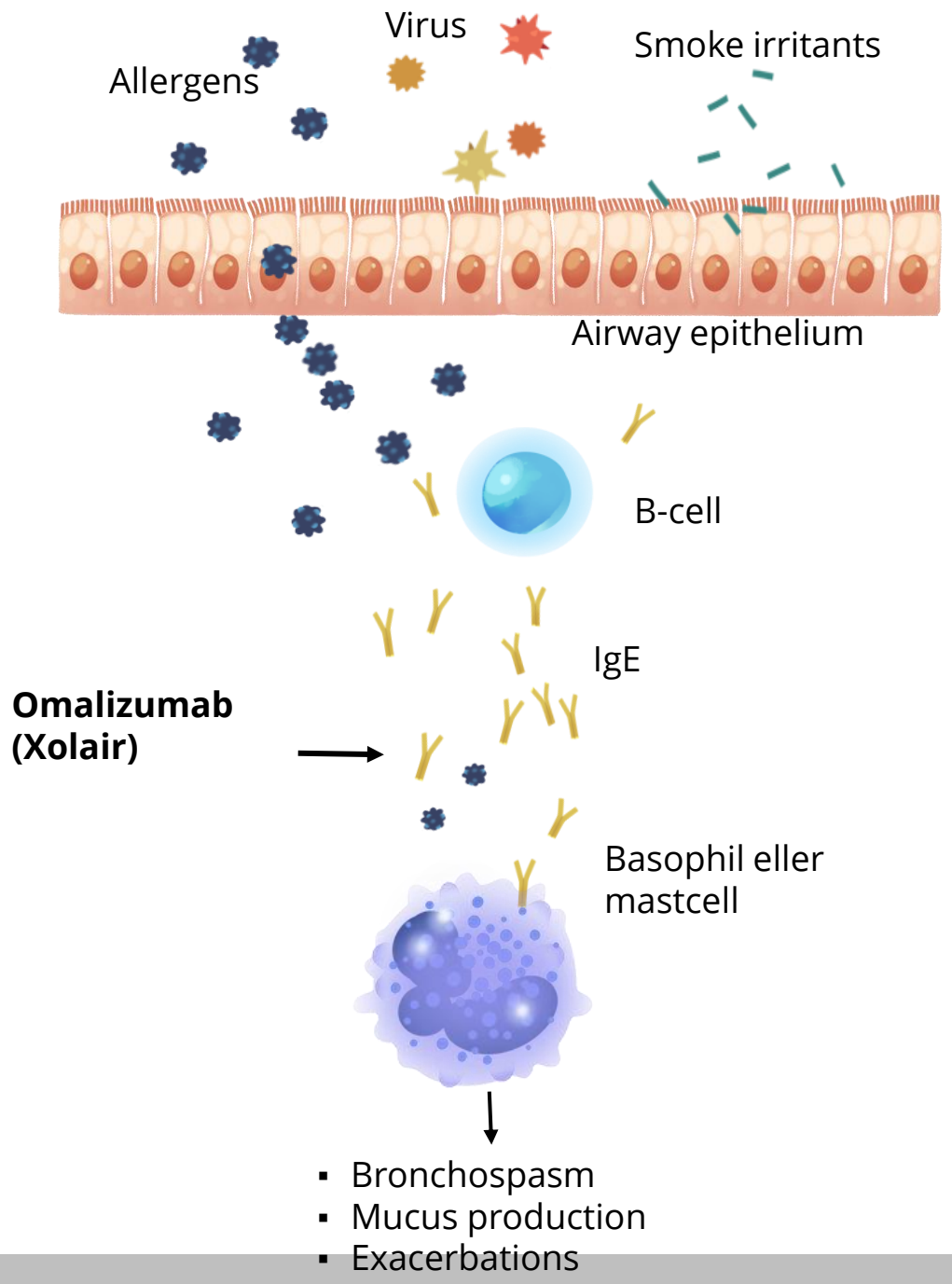
Indications*

- Severe asthma and
- exacerbations or daily OCS use
- perennial atopy combined with allergen induced symptoms
- total IgE within dose range

*specific criteria may vary by country

Effect on biomarkers

- No currently available biomarkers



NSAN

Clinical effects

- Reduce exacerbations
- Reduce OCS use

In individual patients may be seen:

- Improve lung function
- Improve symptoms

Predictors of treatment response

- Allergic driven disease
- Atopy (positive SPT/specific IgE)
- Exacerbations
- Childhood onset asthma
- FeNO≥20 ppb

Ref:Holguin et al, Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J 2020; 55; 1900588

Anti-IL5/IL5R

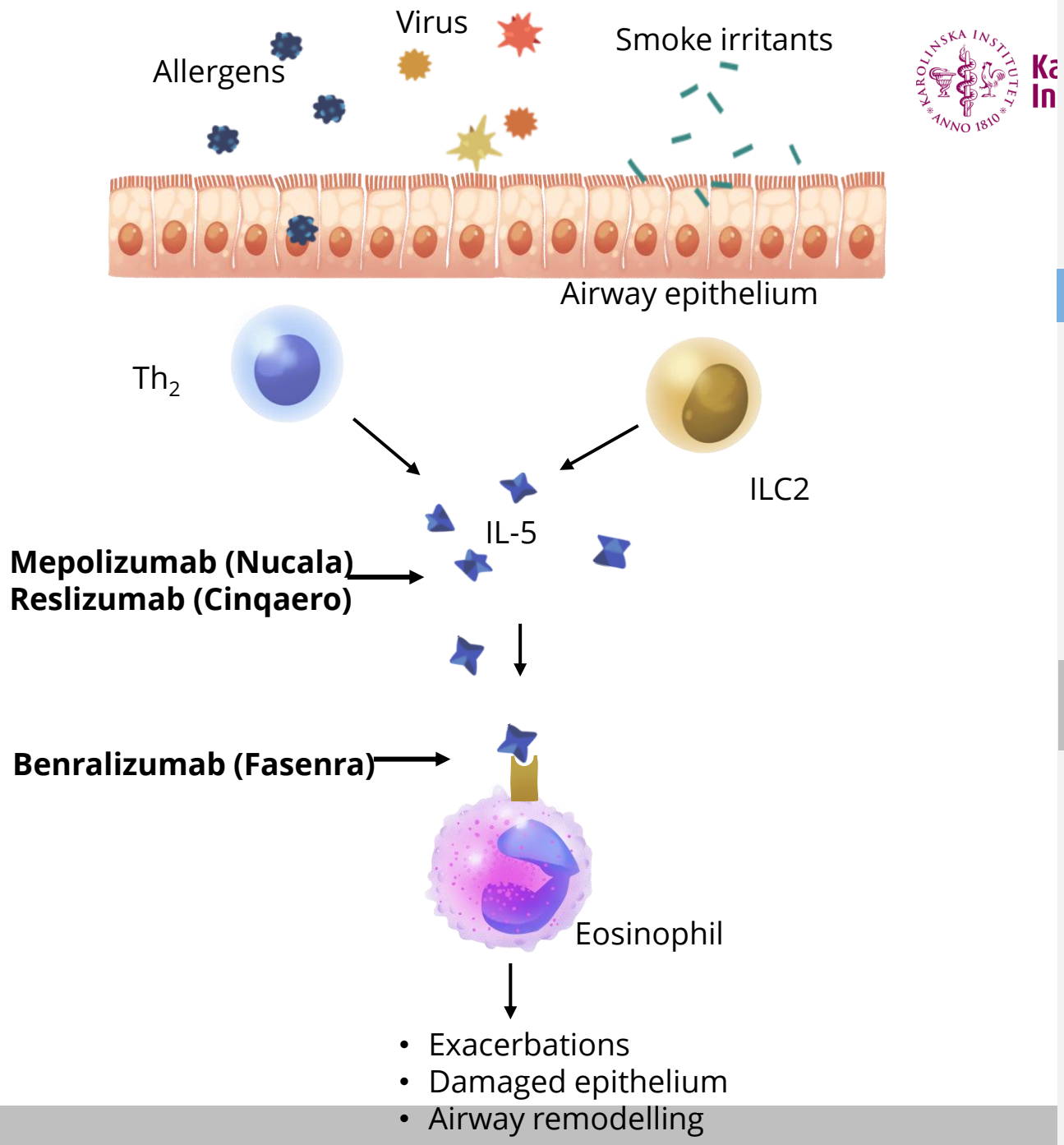
Indications*

- Severe asthma and
- exacerbations or daily OCS use
- and increased eosinophils

*specific criteria may vary by country

Effect on biomarkers

- Reduce eosinophils



Clinical effects

- Reduce exacerbations
- Reduce OCS use

In individual patients may be seen:

- Improve lung function
- Improve symptoms

Predictors of treatment response

- High blood eosinophils
- Exacerbations
- Adult onset asthma
- Nasal polyposis

Ref:Holguin et al, Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J 2020; 55; 1900588

Anti-IL4R

Indications*

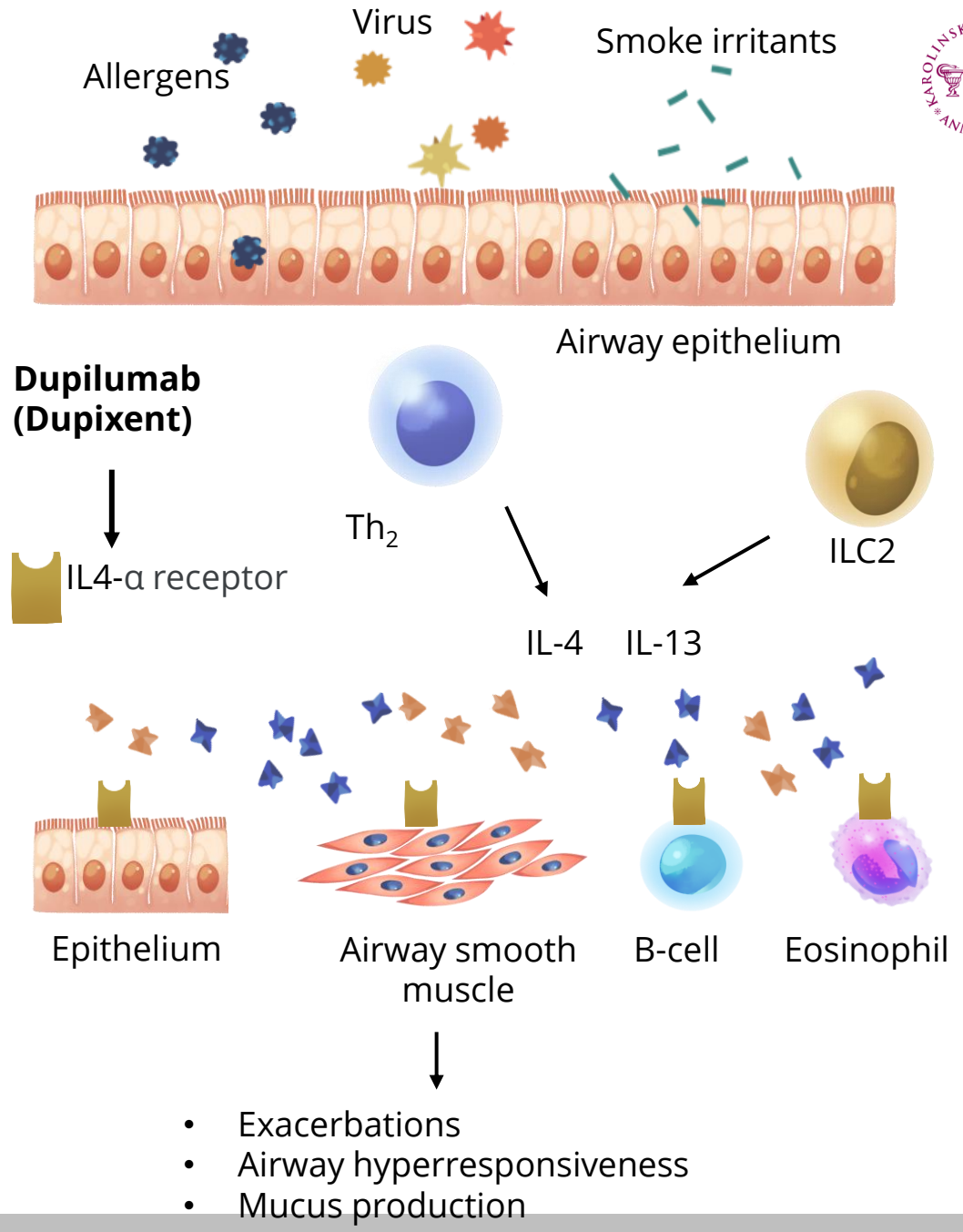
Severe asthma and *either*
- Exacerbations and increased eosinophils or FeNO

or
- daily use of OCS

*specific criteria may vary by country

Effect on biomarkers

- Reduce FeNO
- Reduce IgE
- Increase blood-eosinophils



Ref:Holguin et al, Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline. Eur Respir J 2020; 55; 1900588

NSAN

Clinical effects

- Reduce exacerbations
- Reduce OCS use
- Reduce nasal polyposis

In individual patients may be seen:
- Improve lung function
- Improve symptoms

Predictors of treatment response

- High blood eosinophils
- High FeNO
- Exacerbations
- Nasal polyposis/atopic dermatitis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

Phase II

Patients with severe asthma on high dose of inhaled steroids

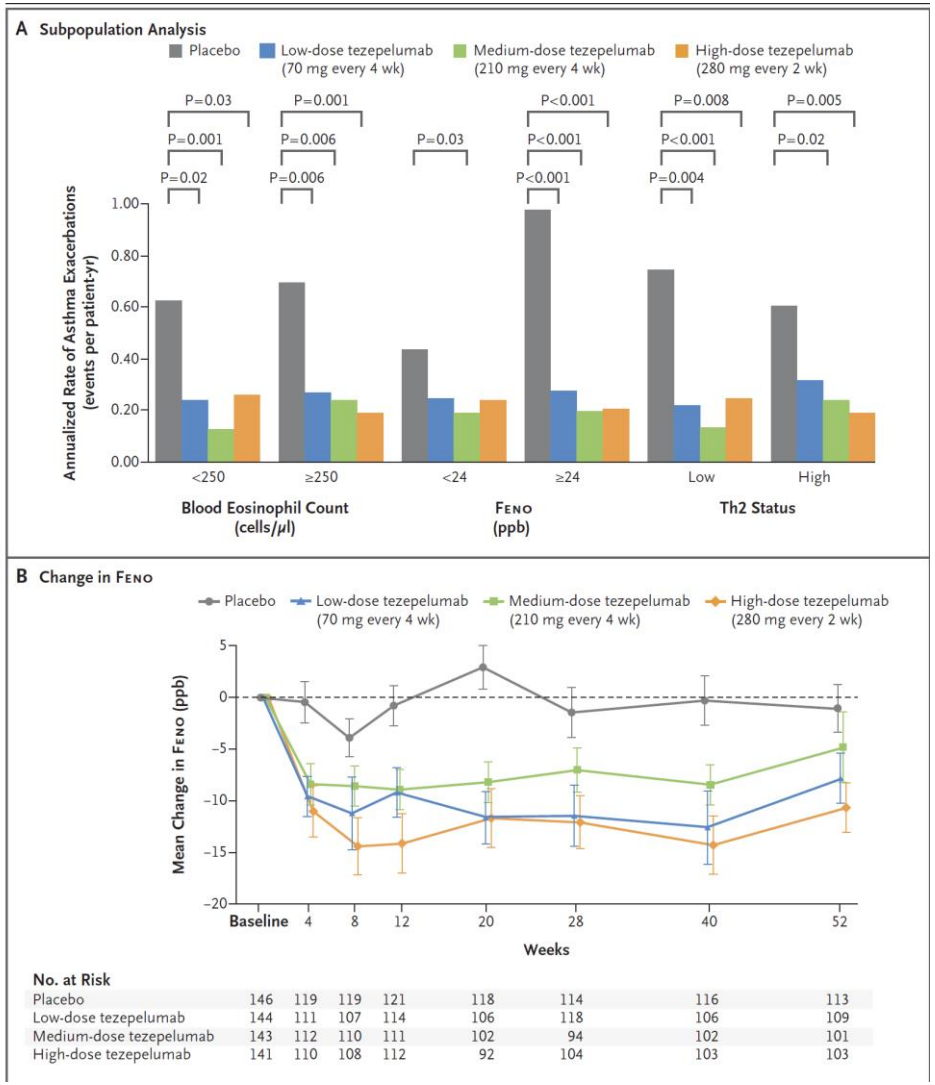
Two or more exacerbations need OCS or 1 needs hospitalization

FEV1 between 40%-80%

ACQ-6 : 1.5

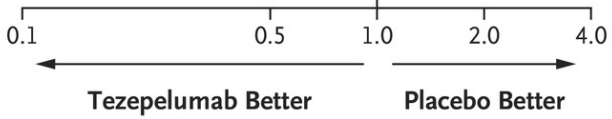
Telezumab (low/medium/high dose/placebo)

Outcome: exacerbation no at week 52



Anti-TSLP

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FeNO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FeNO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

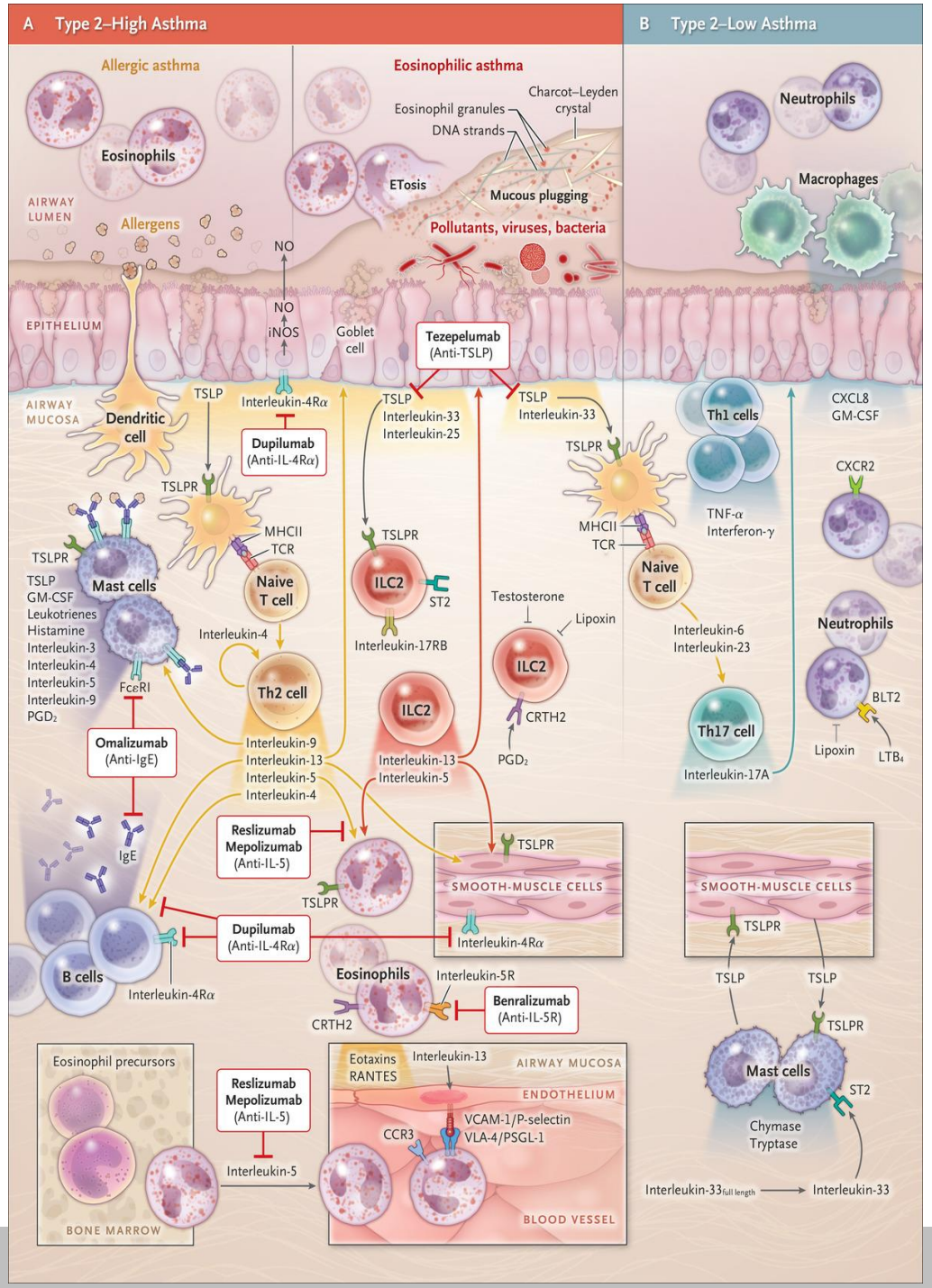
Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

1061 adults and adolescences with ≥ 2 exacerbations last year.

210 mg (medium dose) /placebo every 4 weeks for 52 weeks.

Exacerbations-rate



Svår astma biologisk behandling mål idag och imorgon

☺

Brusselle GG,et al, N Engl J Med 2022

Svår astmamotatgning

Hur gör man?

Multidisciplinär team

- Sjuksköterska
- Sjukgymnast
- Kurator
- Läkare

Astma fenotyp och svårighet?

- Anamnes
- B celler, elfores, ANA/ANCA
- IgG subklasser
- CT
- Klin-fys
- ÖNH
- Reuma?
- Hematologen?

Är det bara astma ? /Differentialdiagnoser

- KOL
- Trakeobronkomalaci/Excessive Dynamic Airway Collapse (EDAC)
- Bronkiektasier, Cystisk fibros
- Kronisk lungembolism, Hypereosinofil syndrom
- EGPA (Eosinofil Granulomatos med PolyAngit), IgG4 relaterad sjukdom
- ABPA, allergisk alveolit, obliterativ bronkiolit
- Lungfibros, tumör, främmande kropp
- Hjärtsvikt, panikångest, hyperventilation
- VOC (Vocal Cord Dysfunction)/EILO (exercise induced laryngeal obstruction)
- Sarkoidos, PAH, tbc

Följande stegs

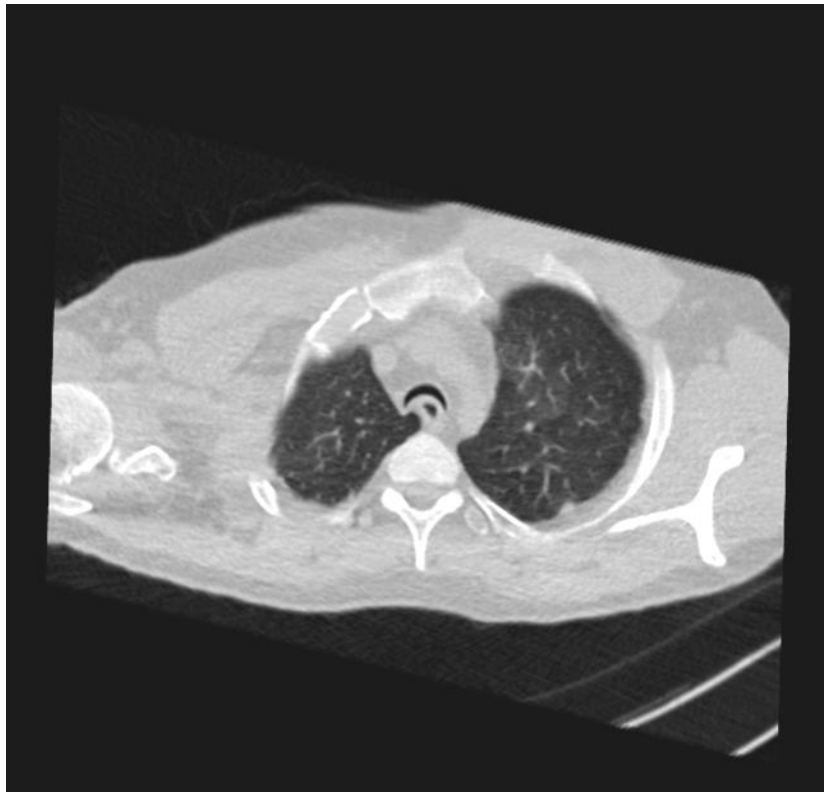
- Behandling optimering
- Samsjuklikheter
- Uppföljning
- Konferens

”Svår” astma - samsjuklikhet

- Kvinna 50 år
- Allergisk astma sedan tonåren (pälsdjur, björk).
- ICS/LABA. Stabil ” tom ca 5 år tillbaka , försämras sedan med kraftig dyspné vid ansträngning, flera exacerbationer.
- Ökning av ICS, LABA, LAMA, LTRA , tillägg av theofylamin.
- Prova omalizumab och OCS kontinuerligt utan stor effekt.

”Svår” astma - samsjuklikhet forts.

Extensive utredning bland annat med CT vid dynamisk-utandning.

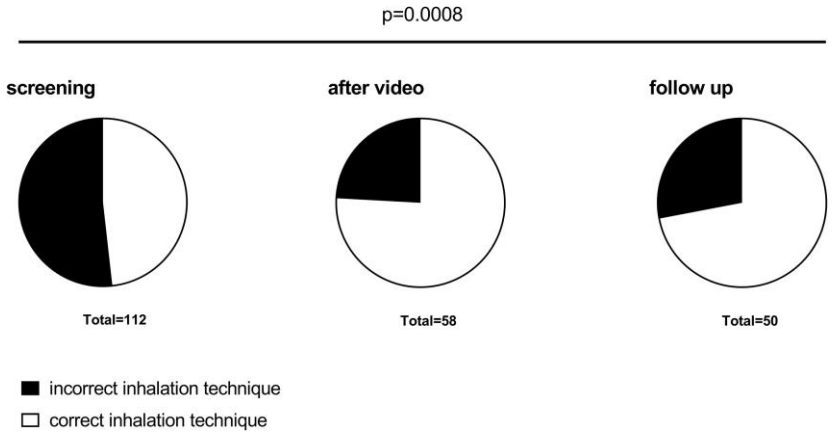


Compliance

- Få patienter sina mediciner?
- Få han/hon rätt?
- Andra problem?

Optimering av inhalation teknik

Müller T, Müller A, Hübel C, Knipel V, Windisch W, Cornelissen CG, Dreher M. Optimizing inhalation technique using web-based videos in obstructive lung diseases. Respir Med. 2017 Aug;129:140-144. doi: 10.1016/j.rmed.2017.06.009. Epub 2017 Jun 17. PMID: 28732821.



Highlights

- Incorrect inhalation technique was common among patients with airway diseases.
- Training videos provided by the German Airway League were understood by 88% of the patients.
- After watching the video 76% of patients with incorrect inhaler use demonstrated correct inhaler use.
- 72% of patients still used their inhalation devices correctly at follow-up.

”Svår” astma - optimering

- Pat 70 år, ex-rökare .
- Dyspné sedan 15 år tillbaka, mest vid ansträngning , ej allergi.
- ICS/LABA , viss effekt, upp till 5 ggr/dagligen. Provat olika inhalationer, ink LAMA, mest pulver. Utan effekt
- Eos mellan 0,6-0,9.
- OCS > 4 ggr per år

Förlopp

Nybesök:

- FeNO över 100 , FEV1 80 % , eos > 0,6

Optimering:

- Ges Alvesco 2+2 med spacer och Innovair 1+1, LTRA 1+1
- Efter 6 månader, FeNO under 25 , ACT 23 ,FEV1 ökat, eos < 0,5
- Gå ner i behandling trappa med hög dos ICS/LABA
- Ej behov av OCS

Allergisk astma

- Man 50 år. Allergisk astma sedan barndomen

<u>Nybesök 15 år tillbaka</u>

- IgE mellan 150-200, SPT : +ve för pälsdjur, även ägg.
- FEV1 ca 80% av Förväntad, FEV1 kvot > 70
- Eos < 0,3 x 10E9

- ICS+LABA högt dos plus extra LABA **(mycket)!!!,** Theodur, Inh Combivent, frekventa exacerbationer med OCS och även inläggningar.

Allergisk astma forts.

Efter 5 år

- Frekventa exacerbationer , OCS x flera , även provat kontinuerligt
- Utvecklar DM
- FEV1 kvot 60 %
- IgE mellan 140-190.
- Bronkoskopi ej ABPA
- **Startar omalizumab**

- Pat upplever stor skillnad, minskat av exacerbationer kraftigt, ta bort extra LABA, ej behov av OCS . Senaste ACT : 20

Är det eosinofil astma ?

- Följa eosinofiler x flera
- Följa eosinofiler vid försämring/exacerbation
- Följa eosinofiler vid kronisk per oss steroider med dosminskning

Eosinofil astma

- Man ca 30 år gammal
- Ex-rökare, ca 10 pack-år
- Kom med remiss från VC för
- Hosta för ett år, dyspne´, slem. CT uteslutet LE. Bufomix 160 µg/4,5 µg/inhalation 1 x 2.
- Vid nybesök: FVC 1.2 L, 21% av förväntat, **FEV1 1.1 25% av förväntat**, B-eos 3, FeNo 22
- Inläggning för snabbt utredning. (feb 22)

Eosinofil astma cont

- CT : air trappning; Bronkväggförtjockning som minska efter prednisolon 25 mg
- Total IgE 130, Phadiatop negativ
- ANA-ANCA negativ, IgG subklasser ua
- Negativ utredning för allergisk alveolit, Ingen posypos
- Ingen polypos
- Alveco 160; 2+2 & Innovair 100/6 2+2

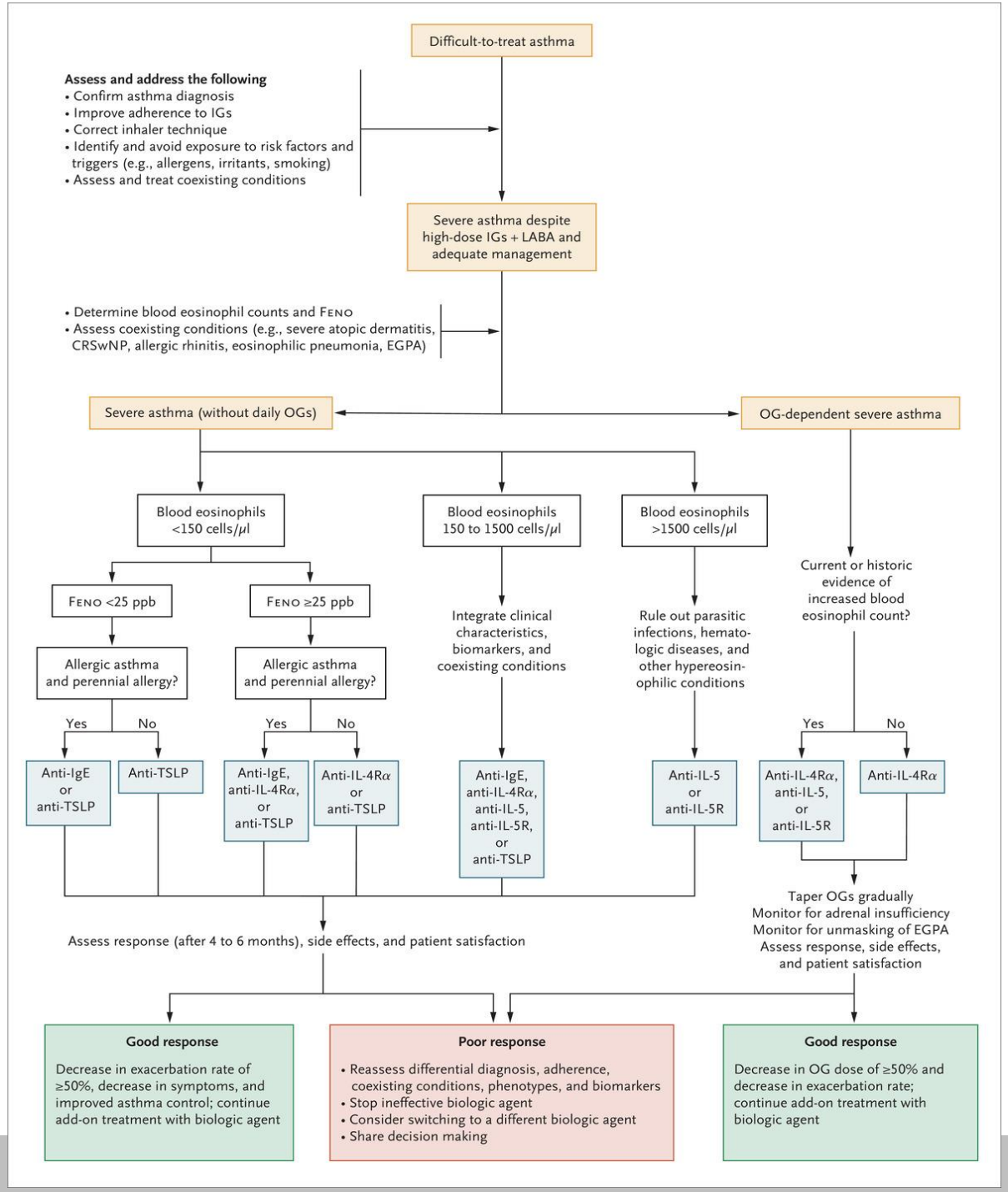
Eosinofil astma cont

- Åb Juni FEV1 4,1 L. B-eos 0,6.
- Åb Sept. FEV1 3,7 L, B-eos 1,4
- Konferens, Godkänt för benralizumab

Start & 4 månader kontroll

- FVC 3,9 L (70 %).
- FEV1 2,4 L (51 %).
- FEV1/FVC 0,61.
- FeNO 19 ppd
- ACT 15
- B-eos 1,8

- FVC 5,65 L (102 %).
- FEV1 4,42 L (95 %).
- FEV1/FVC 0,78.
- FeNO 10 ppd
- ACT 17
- B-eos >0,1 / (från första månad)



Välja rätt biologisk

- Eosinofiller ?
- FeNO ?
- Allergi?
- Nasal polyper?
- Slem?

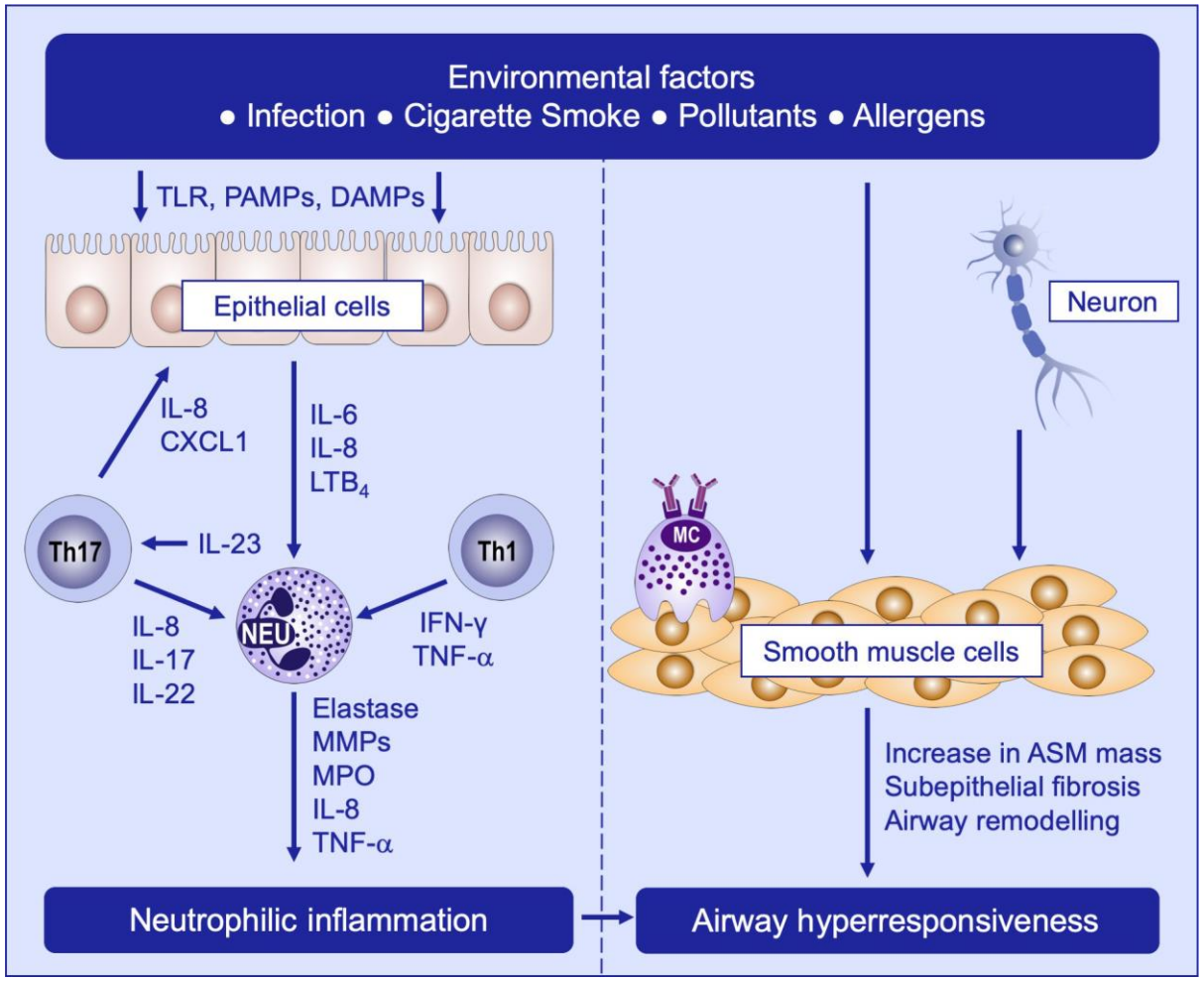
Brusselle GG,et al, N Engl J Med 2022

Undervärdering & Uppföljning

- **At four and 12 m , sen varje 6 m(ssk) & 12 m läkare**
- **Super responders** i.e. : No exacerbations, no OCS, Increase Lung function
- **Responders** : > 50 % reduction of the target (i.e exacerbation/OCS)
- **Poor responders**: < 50 %
- **No-responders**

T2-low asthma : pathophysiology

- Non-T2 airway inflammation; neutrophilia.
- Microbes
- Systemic inflammation associated with obesity and metabolic dysfunction.
- Noninflammatory ; Paucigranolytic asthma
- ASM hypertrophy, Ach is the main neurotransmitter via M3
- Overlapping with T2-high



Sze E. et al Allergy 2020

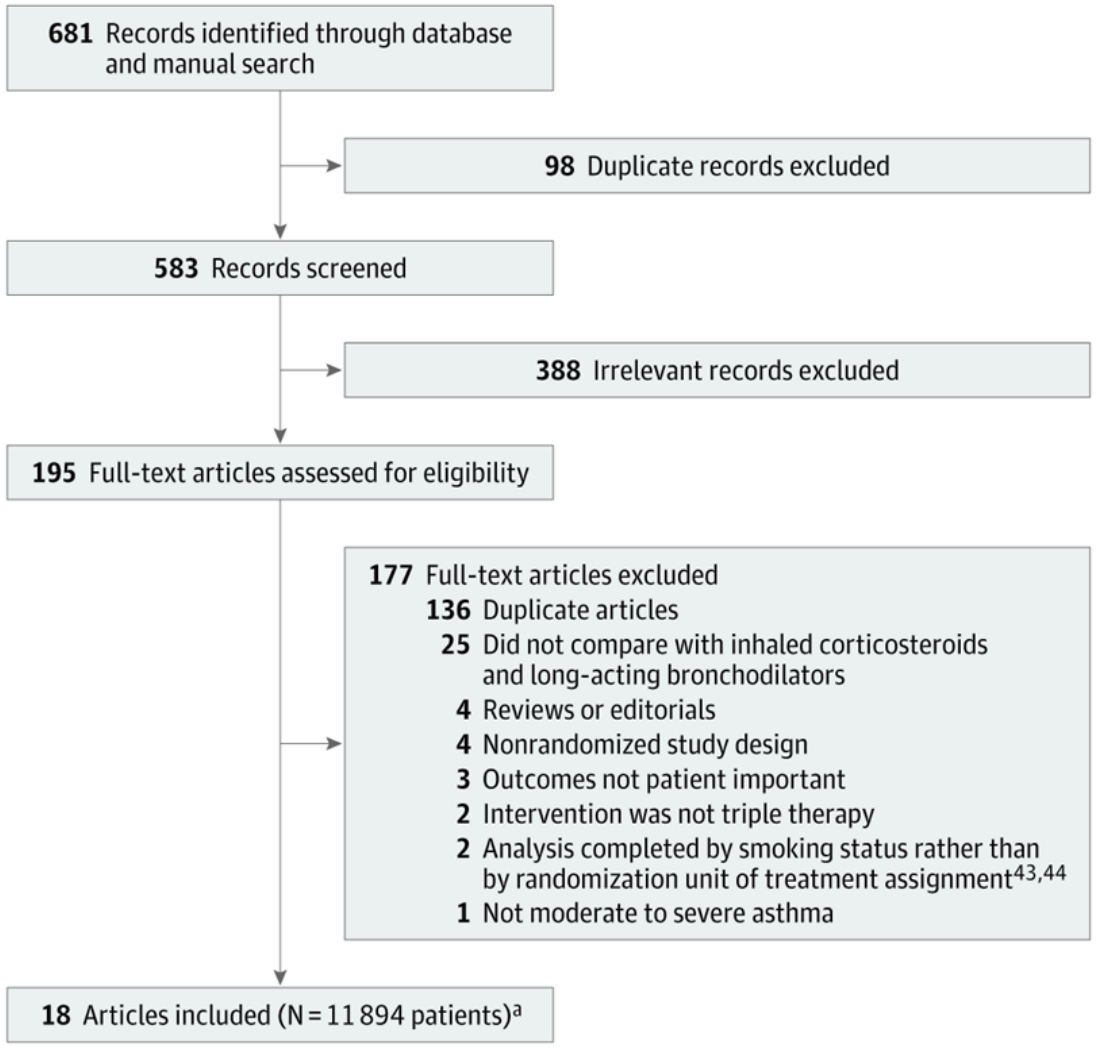
Fitzpatrick AM et al JACI Pract 2020

Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma

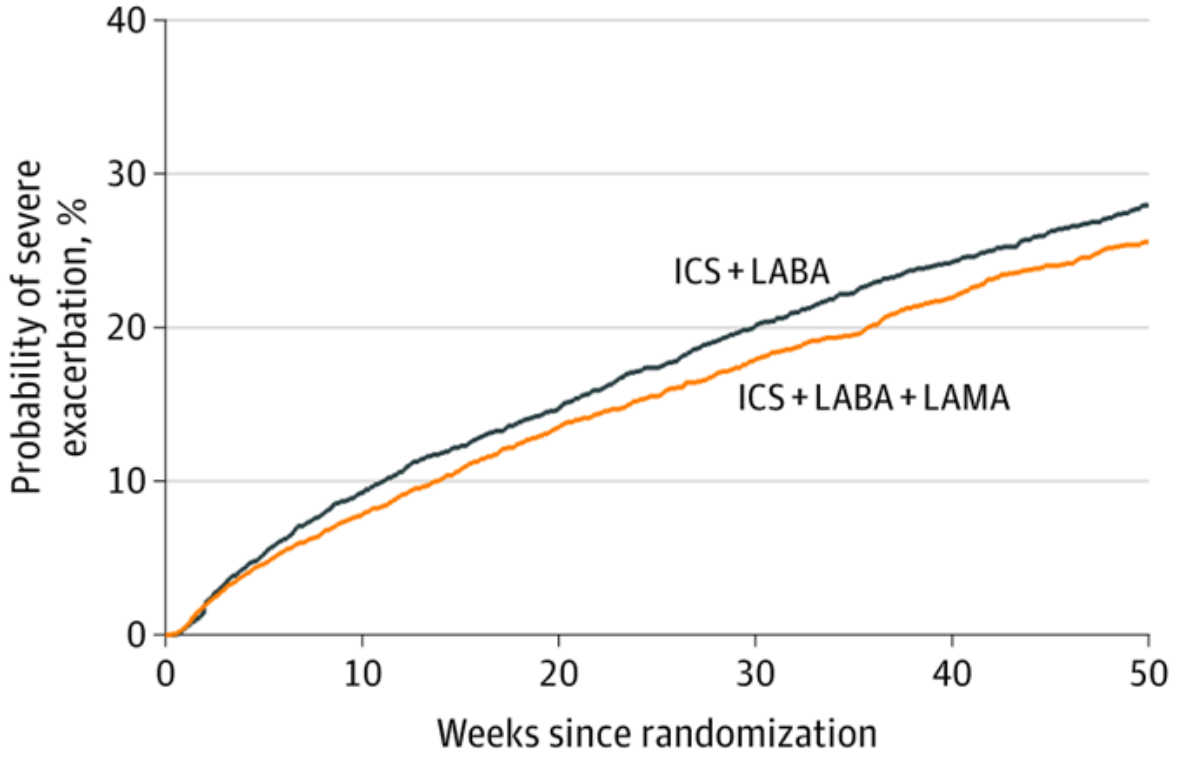
JAMA | Original Investigation

Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma
A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD



Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma-Exacerbations



No. at risk						
ICS + LABA	4137	3650	3320	2922	2540	1760
ICS + LABA + LAMA	4159	3774	3396	2871	2332	1475
No. of studies	6	6	6	6	6	4

Immunomodulatory effects of

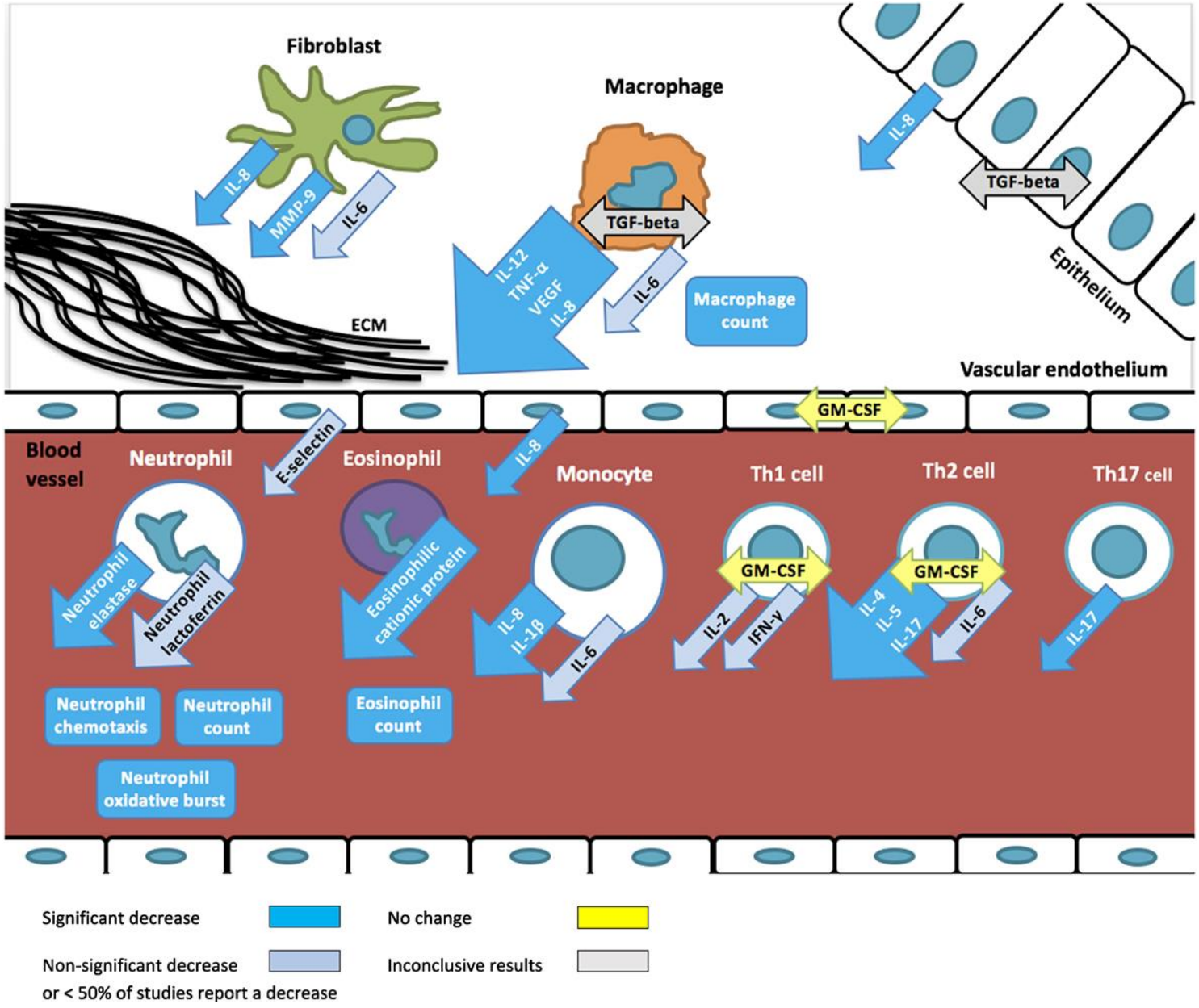
frontiers in Immunology

SYSTEMATIC REVIEW
published: 13 March 2018
doi: 10.3389/fimmu.2018.00302

The Immunomodulatory Effects of Macrolides—A Systematic Review of the Underlying Mechanisms

Petra Zimmermann[1,2,3,4], Victoria C. Ziesenitz[5], Nigel Curtis[1,2,3] and Nicole Ritz[2,4,5]*

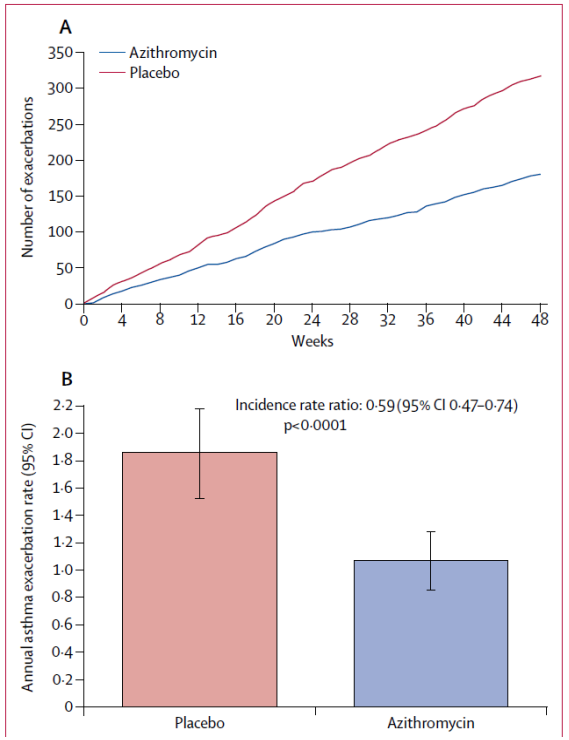
Systematic review, 22 RCT using one of four macrolides as intervention (azithromycin, clarithromycin, erythromycin, and roxithromycin) in human inflammatory diseases



Azitromycin i astma, AMAZES study.

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson



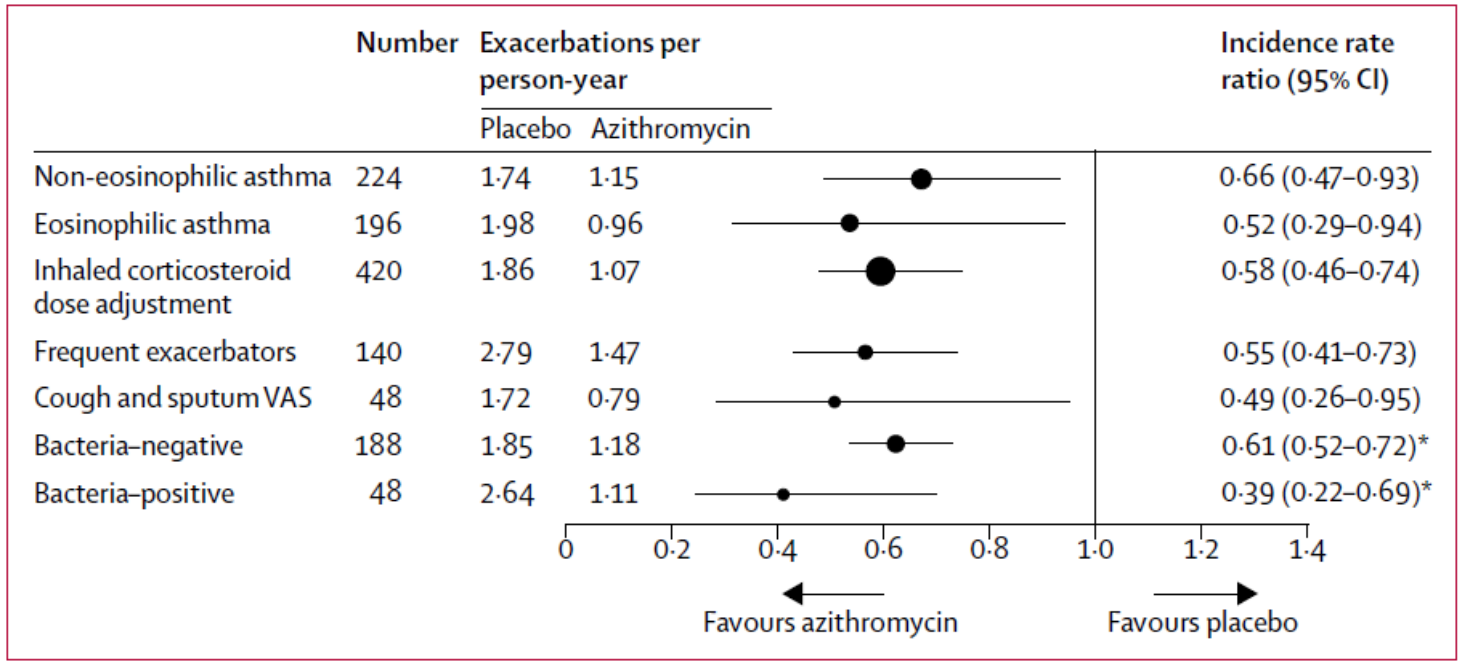


Figure 3: **Effect of add-on azithromycin treatment on asthma exacerbations according to prespecified subgroup analyses**

Inhaled corticosteroid dose adjustment adjusted for maintenance inhaled corticosteroid dose at baseline (low, medium, or high). Non-eosinophilic asthma defined by baseline sputum eosinophil count less than 3% or blood eosinophil count less than 300 per µL if sputum unavailable. Eosinophilic asthma defined by baseline sputum eosinophil count of 3% or more, or blood eosinophil count greater than 300 per µL if sputum unavailable. VAS=visual analogue scale. *Significant interaction between subgroup and treatment.

Gibson P. , et al Lancet 2017

Sammanfattning

- Svår astma finns mellan oss
- Det behövs ordentligt utredning, och uppföljning
- DVS : tid och tålamod, från både patienter och vårdpersonal ☺
- Svår astmamottagning

Sammanfattning forts.

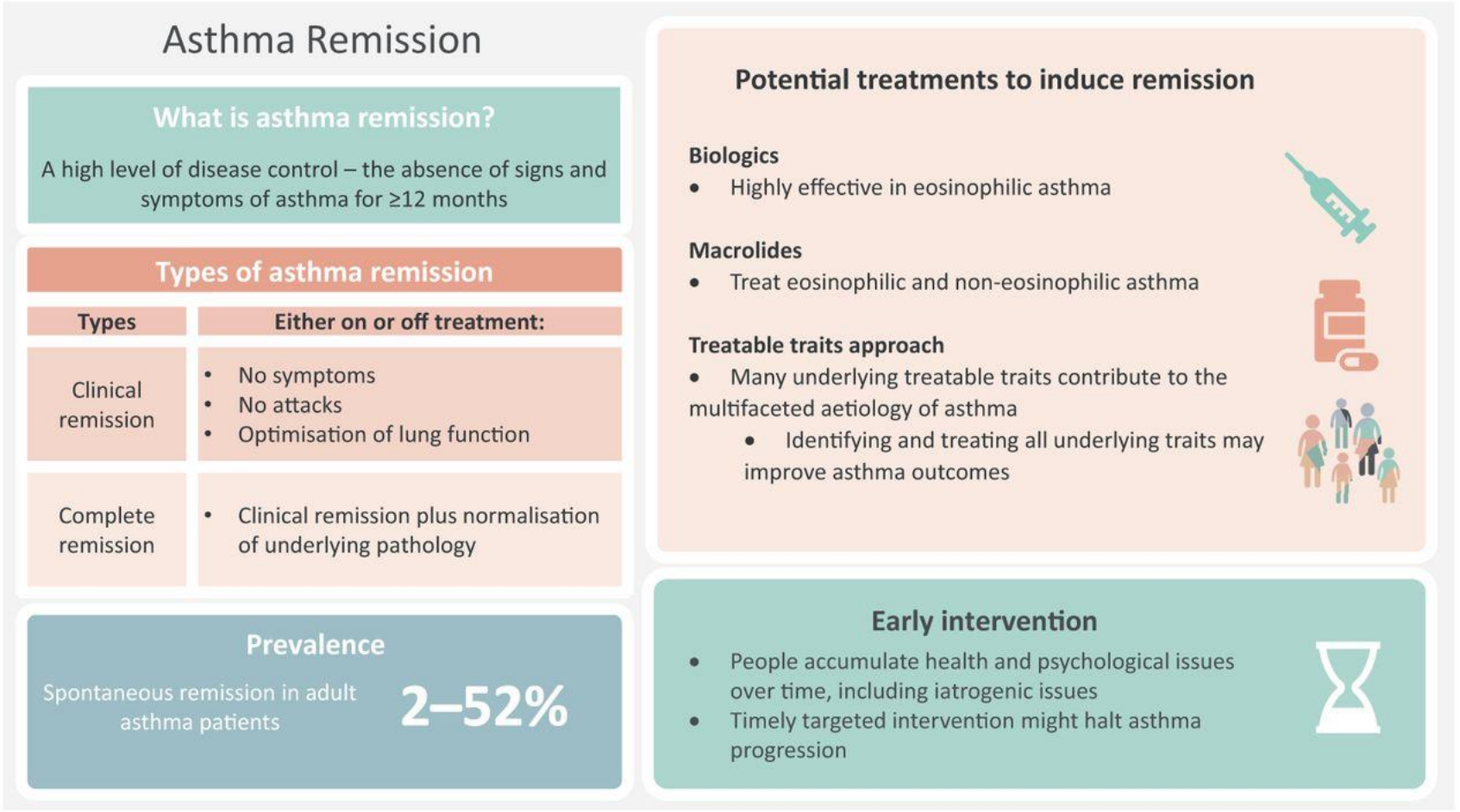
- **Innan**
- Läkemedelsbehandling, inhalationsteknik, compliance

- Uppföljning med B-celler vid lugnt skede samt vid exacerbationer

- Om behövs trappa upp i behandling

- **Ingen patient i kontinuerling OCS**

A visual summary of remission.



Dennis Thomas et al. Eur Respir J 2022;60:2102583

Huddinge

Nafpaktos

Tack!