Optimized Treatment in Severe Asthma
Real World Case Sharing

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振興醫療財團法人 振興醫院

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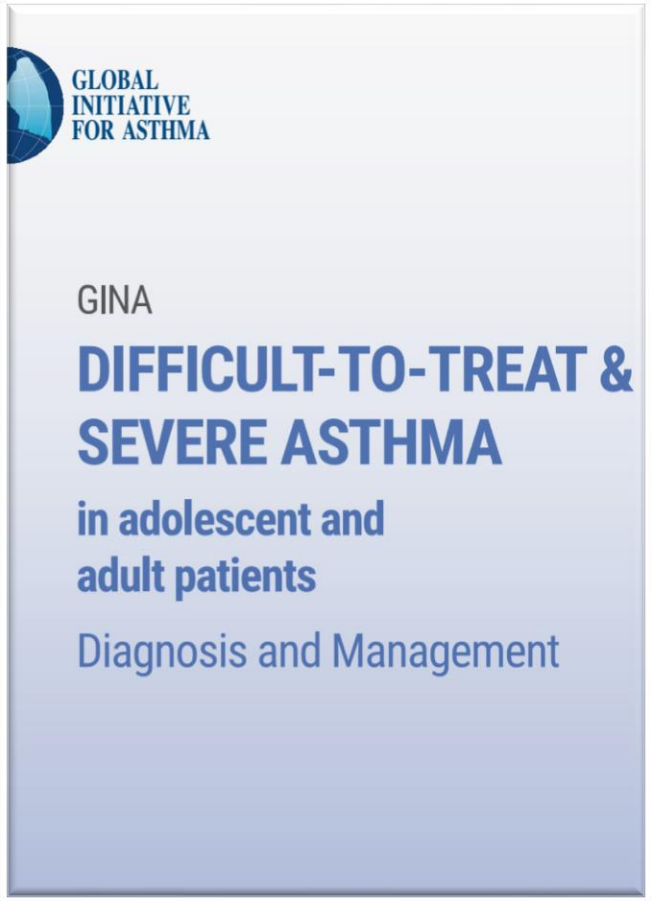


Uncontrolled asthma: ≥1 of the following:

- **Poor symptom control** (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
- **Frequent exacerbations** (≥2/year) requiring oral corticosteroids (OCS), or **serious exacerbations** (≥1/year) requiring hospitalization

24~50%

Difficult-to-treat asthma:

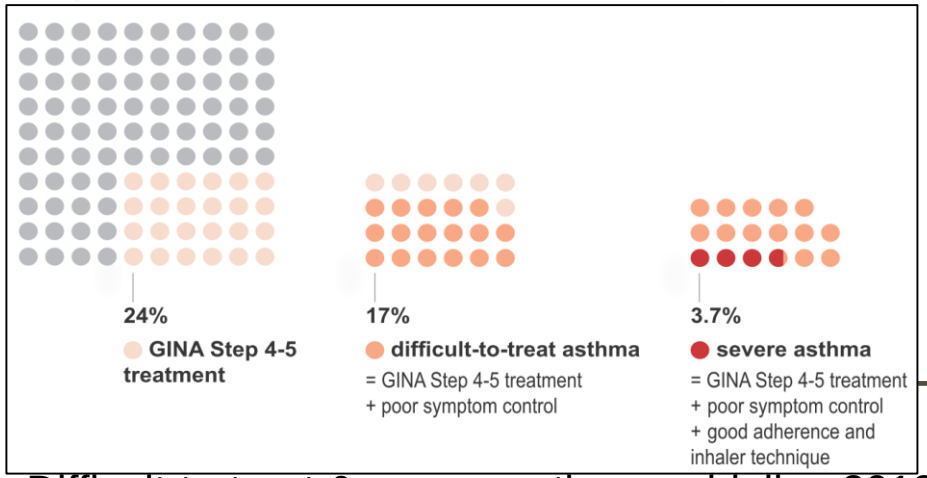
- **Uncontrolled** despite GINA Step 4/5 treatment (e.g. medium/high dose ICS with a second controller; maintenance OCS), *or*
- **Requiring** such treatment to **maintain** good symptom control and reduce the risk of exacerbations.

~17%

Severe asthma: (a retrospective label)

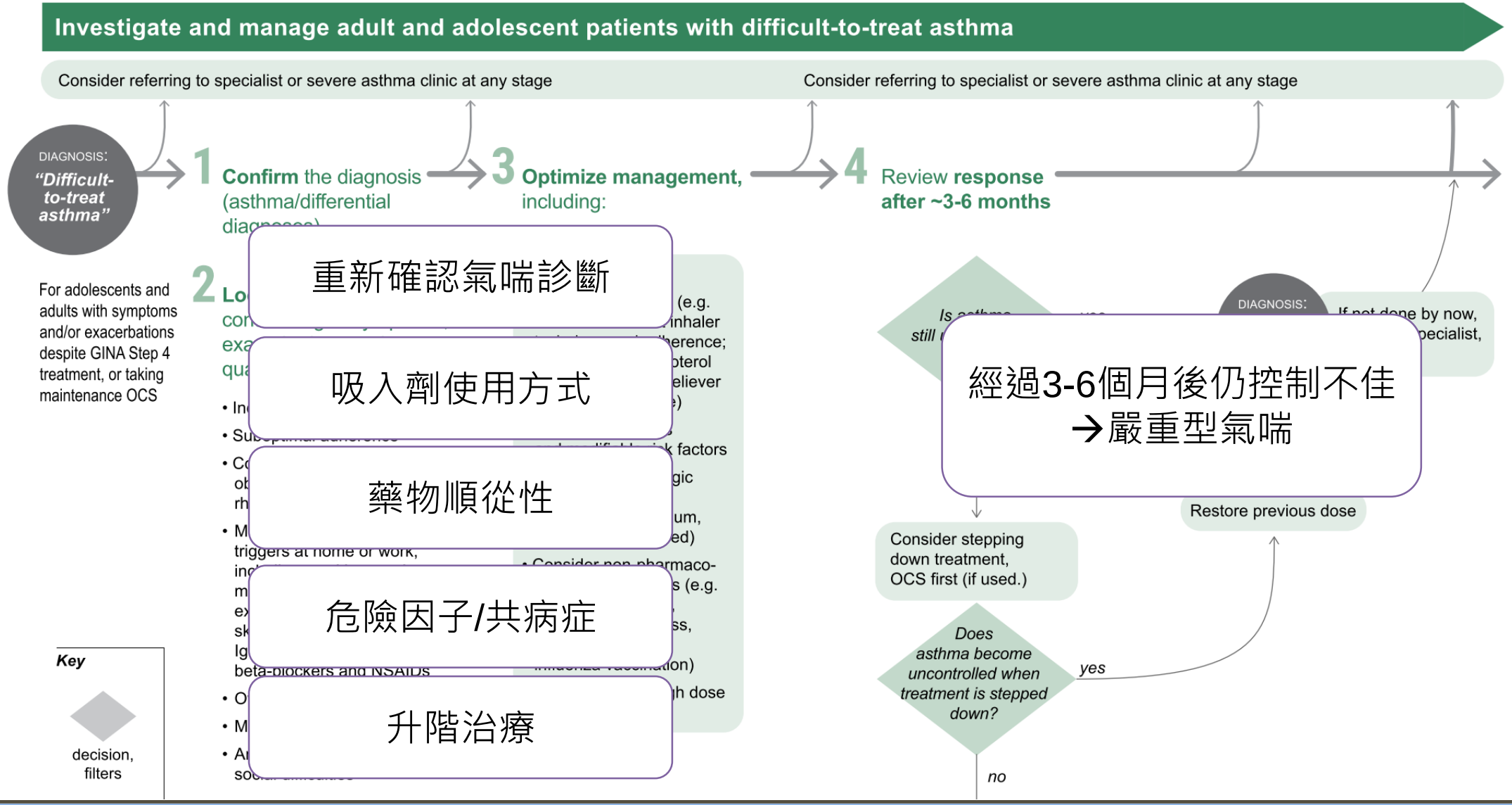
- **Uncontrolled** despite adherence with maximal optimized therapy and treatment of contributory factors, *or*
- **Worsens** when high dose treatment is decreased.

5-10%



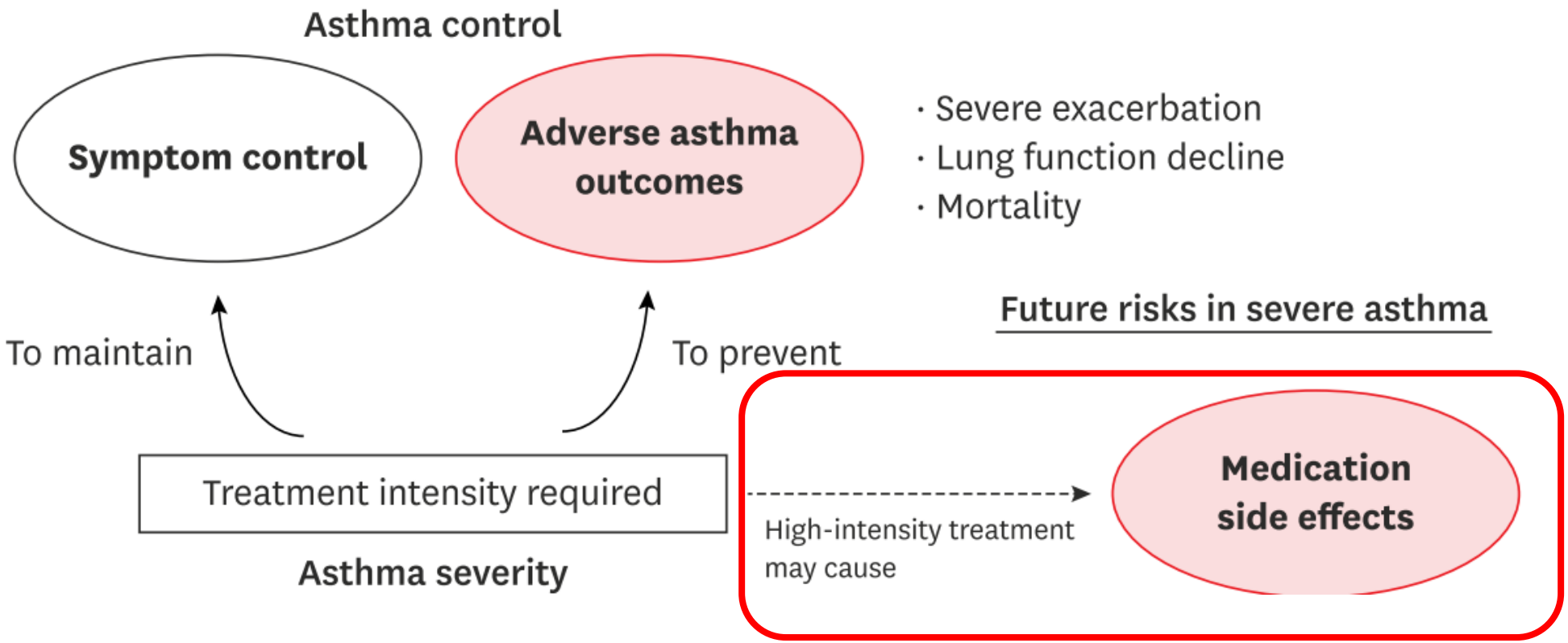
Difficult-to-treat & severe asthma guideline 2019

Management of difficult-to-treat asthma



Difficult-to-treat & severe asthma in adolescent and adult patients. Diagnosis and Management

Long-term OCS related to future risks in severe asthma

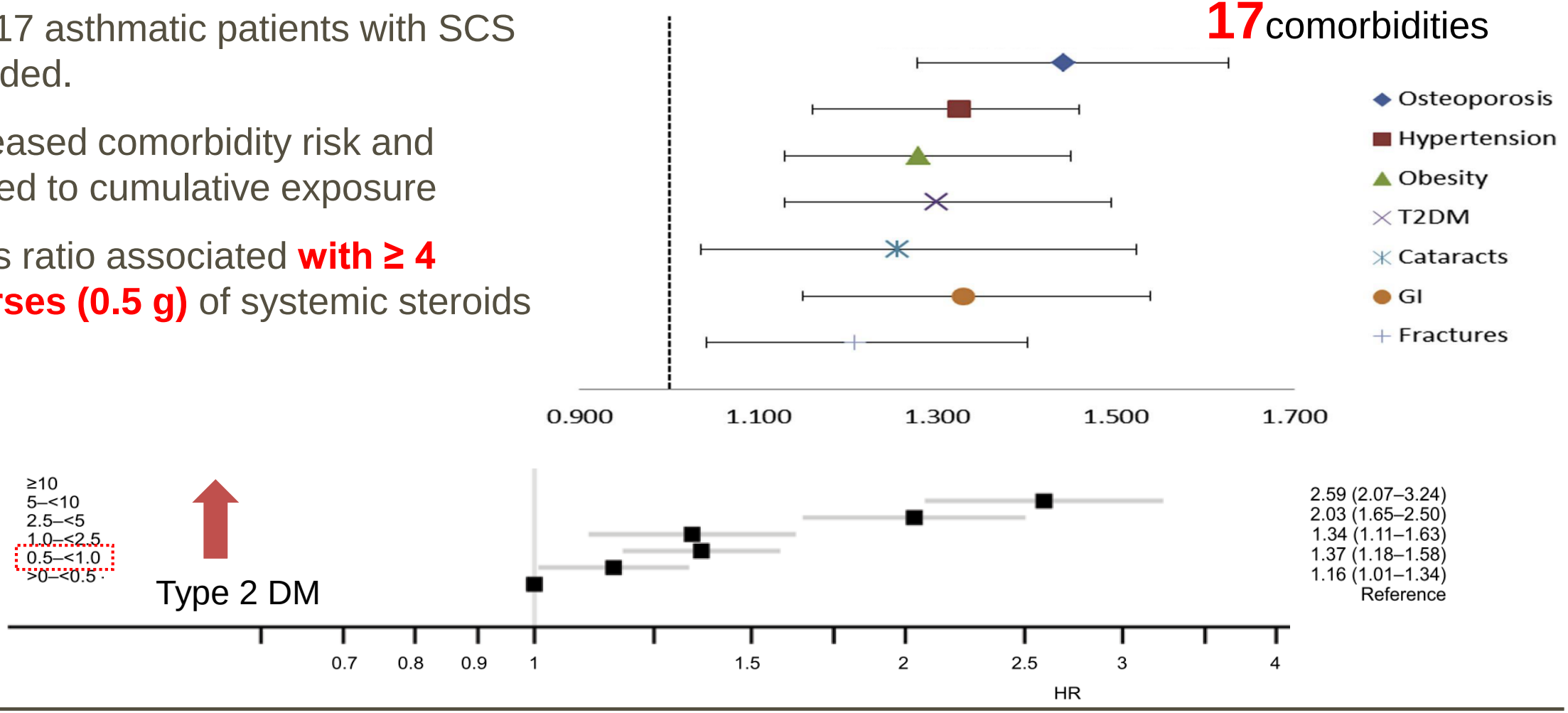


Allergy Asthma Immunol Res. 2019;11(6):763-778

Dose-response relationship between cumulative systemic corticosteroid use and risk of side effects in asthma

UK database

- 24,117 asthmatic patients with SCS included.
- Increased comorbidity risk and related to cumulative exposure
- Odds ratio associated **with ≥ 4 courses (0.5 g)** of systemic steroids



J Asthma Allergy 2018:11 193–204

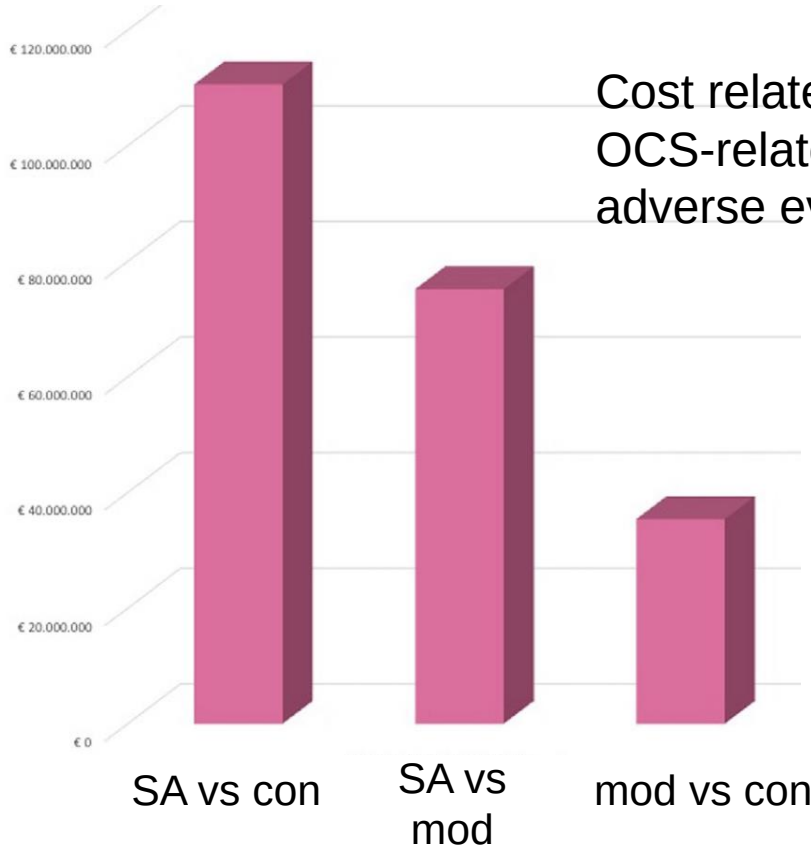
Modefied from Sullivam, JACI 2017

High cost of corticosteroids-related comorbidities

Severe Asthma Network in Italy (SANI) registry

- Severe asthma population: 5%
- Severe asthma **treated with OCS: 62%**

Comorbidity	Non-asthma control	Moderate asthma	Severe asthma
Type II diabetes	€ 83,49	€ 97,40	€ 139,15
Obesity (BMI >30)	€ 404,30	€ 615,24	€ 738,29
Osteopenia	€ 18,81	€ 18,81	€ 94,03
Osteoporosis	€ 31,13	€ 41,51	€ 166,05
Fracture	€ 79,40	€ 59,55	€ 99,25
Dyspeptic disorders	€ 230,04	€ 325,89	€ 623,03
Glaucoma	€ 31,53	€ 31,53	€ 42,04
Cataract	€ 42,04	€ 52,55	€ 94,60
Cardiovascular disease	€ 146,78	€ 146,78	€ 209,68
Hypertension	€ 240,84	€ 279,38	€ 327,54
Psychiatric disorders	€ 485,45	€ 601,96	€ 737,89
Hypercholesterolaemia	€ 47,13	€ 59,98	€ 64,26
Sleep disorder	€ 28,18	€ 35,22	€ 56,36
Chronic kidney disease	€ 261,41	€ 336,10	€ 522,83
Total for 2-year analysis	€ 2130.54	€ 2701.91	€ 3915.00
Annual total cost	1065.27 €	1350.96 €	1957.50 €

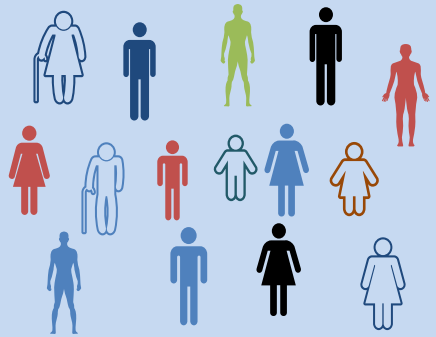


Cost related to OCS-related adverse events

World Allergy Organization Journal 2019;12:100007

Severe asthma requiring a personalised treatment approach

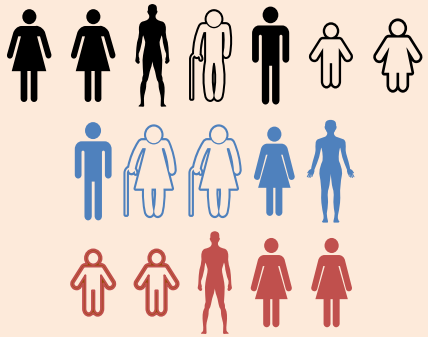
Heterogeneity and complexity



There is no ‘one size fits all’ treatment for severe asthma[1–3]

Phenotyping identifies clinically distinct patient groups …[1,4]

Phenotyping



… who share clinical and/or pathological characteristics …[1,5]

Personalised treatment

… leading to a more personalised and predictive treatment approach[1,2,4]

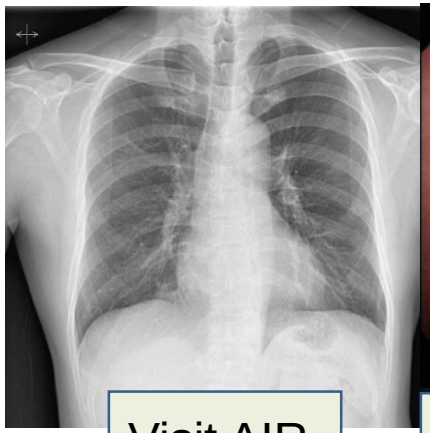
Rapidly increasing selection of biologics available for treatment of severe asthma necessitates better-informed decision-making

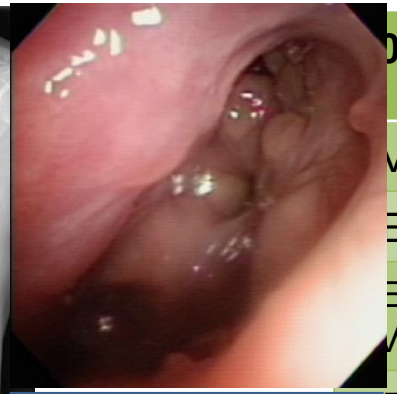
1. Wenzel SE. *Nat Med*. 2012;18:716–725; 2. Fajt ML & Wenzel SE. *Allergy Asthma Immunol Res.* 2017;9:3–14; 3. GINA. Global Strategy for Asthma Management and Prevention. 2018. Available from: ginasthma.org [accessed May 2019]; 4. Guilleminault L, et al. *Eur Respir Rev.* 2017;26:160010; 5. Wenzel S. *Clin Exp Allergy*. 2012;42:650–658.

Mr. Chen's problems

- 51 years old, married
- Height: 174 cm Body Weight: 74kg
- Future contract employee
- Never smoker; No keep pets
- Medical history:
  - Asthma for 6 years
  - Chronic paranasal sinusitis with polyposis s/p pansinusectomy and septoplasty

- Shortness of breathing and chest tightness for 3 days
- Progressed dyspnea and wheezing occurred at midnight
- Visit ER and received bronchodilator via nebulizer, IV steroid and abx treatment
- Transferred from ER to our clinic for poor asthma control on 2018/2/22





01308	201610	Pre	% pred	Post	% CHG
VC	FVC	3.63L	85%	3.60(84%)	-1%
EV1	FEV1	2.44 L	72%	2.30(68%)	-6%
EV1/ VC	FEV1/ FVC	67		64	
EF	PEF	7.76	81%	6.18(64%)	2%

Visit AIR clinics

pansinusectomy and septoplasty

prednisolone 1~2 tab qd~bid and PRN

201308 **201608** **201702** **201711** **201802**

Cough with
Wheezing, night
Total IgE 296, Eo
No aller

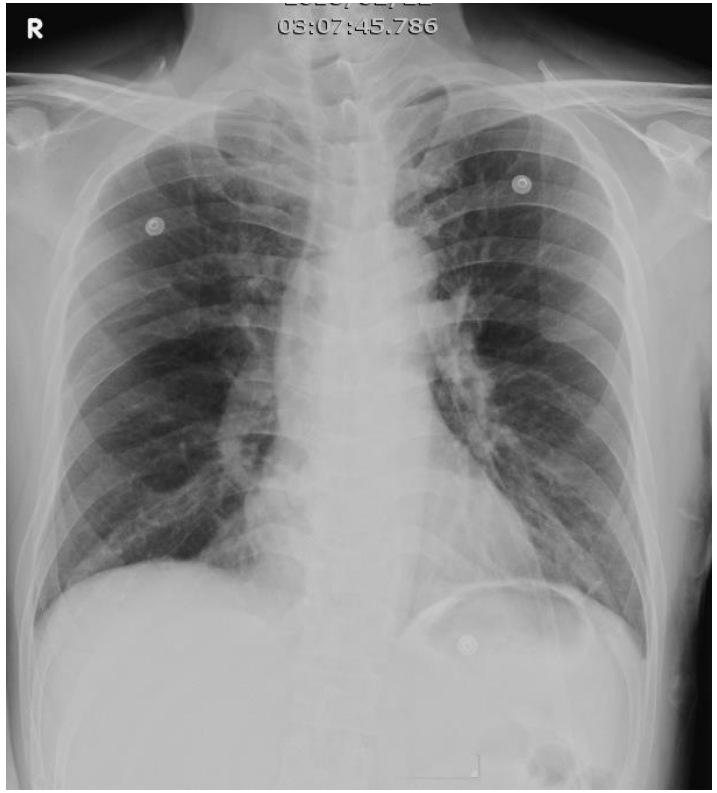
Purule
V
Chr

- Easy got common cold
- Severe AE and went to ER on 2017/02
- Nasal polyps recurred on 201611
- **Feel poor control**

Yellow sputum for 2 weeks

Budesonide/fomoterol 160/4.5 turb 2 puff bid
theophyllin (200) 1# hs
levocetirizine 1# hs
fluticasone nasal spray qd
montelucast (10)1# hs

Fluticasone/vilanterol (100)1 puff qd
ventolin 2 puff PRN
fexofenadine 1# bid
dexchlorpheniramine (2)1# tid
augmentin (1g)1# q12h



Lab	20180222
WBC	9100
Hb	17.3
PLT	257K
N/L/E	44/44/ **6.5**
CRP	0.29

Clinical course 20180222

- PE: wheezing+
- Asthma attack
- Prednisolone 1# tid
- Unasyn (375) 1# tid
- ventolin PRN and keep Relvar

Follow up 20180226

- No wheezing, but still rhinorrhea and night cough
- Keep prednisolone 1# tid, unasyn 1# tid, xyzal 1# qn, regrow 1# bid, Avamys nasal spray bid
- Eosinophil 592, Total IgE 750
    - Allergen: mite (class 1), Candida (class 1), Cockroach (class 1)

2018 March 8

ACT=10, PEFR 310

FP/Sal evo 250 2 puff bid, tiotropium 2 puff qn+ OCS 1# bid

2018 March 22

PEFR 640

FP/Sal evo 250 2 puff bid, tiotropium 2 puff qn+ OCS 1# qd

2018 March 29

ACT=19,PEFR 560, No SABA

FP/Sal evo 250 2 puff bid, tic

2018 May 17

ACT=11, PEFR 410, ER visit tv

Eos 19%, keep triple therapy

2018 June

6/28 PEFR=500

7/26 ACT=12, PEFR=430

OCS

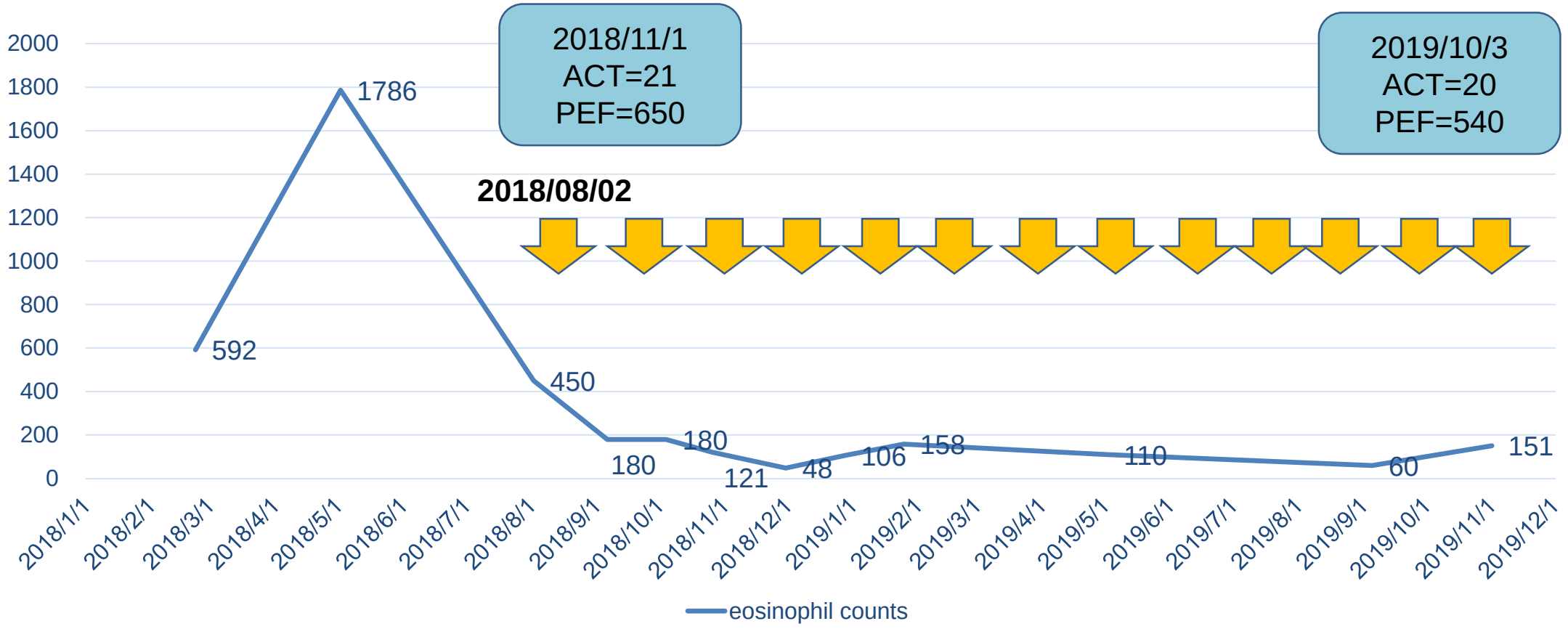
2018 Aug 2

PEFR 470, Eos 450/ul

mepolizumab 100mg sc, self-paid

	201610	201803
Pre-FVC	3.63 (85%)	3.69 (86%)
Pre-FEV1	2.44 (72%)	1.82 (54%)
Post-FVC	3.60 (84%)	4.09 (96%)
Post-FEV1	2.30 (68%)	2.33 (70%)
Post FEV1/FVC	64%	57%
FEV1 BD	-6%	28%
Post-PEF	6.18 (64%)	5.77 (60%)

Traits of eosinophil counts after mepolizumab



Pulmonary function

Nucala use

	201803	201809	201903	201909
Pre-FVC	**3.69 (86%)**	4.03 (95%)	**4.27 (103%)**	**4.32 (102%)**
Pre-FEV1	1.82 (54%)	2.97 (90%)	3.17 (98%)	2.91 (89%)
Post-FVC	4.09 (96%)	4.12 (97%)	4.08 (99%)	4.23 (100%)
Post-FEV1	2.33 (70%)	**3.17 (96%)**	**3.15 (97%)**	**3.05(93%)**
Post FEV1/FVC	**57%**	77%	77%	72%
FEV1 BD	**28%**	7%	-1%	5%
Post-PEF	5.77 (60%)	**8.66 (91%)**	**9.37 (100%)**	**8.34 (88%)**

After 14 courses of mepolizumab:
Fluticasone/salbutamol 125 2 puff bid
fexofenadine 1# bid

Mr. Chen’s problem

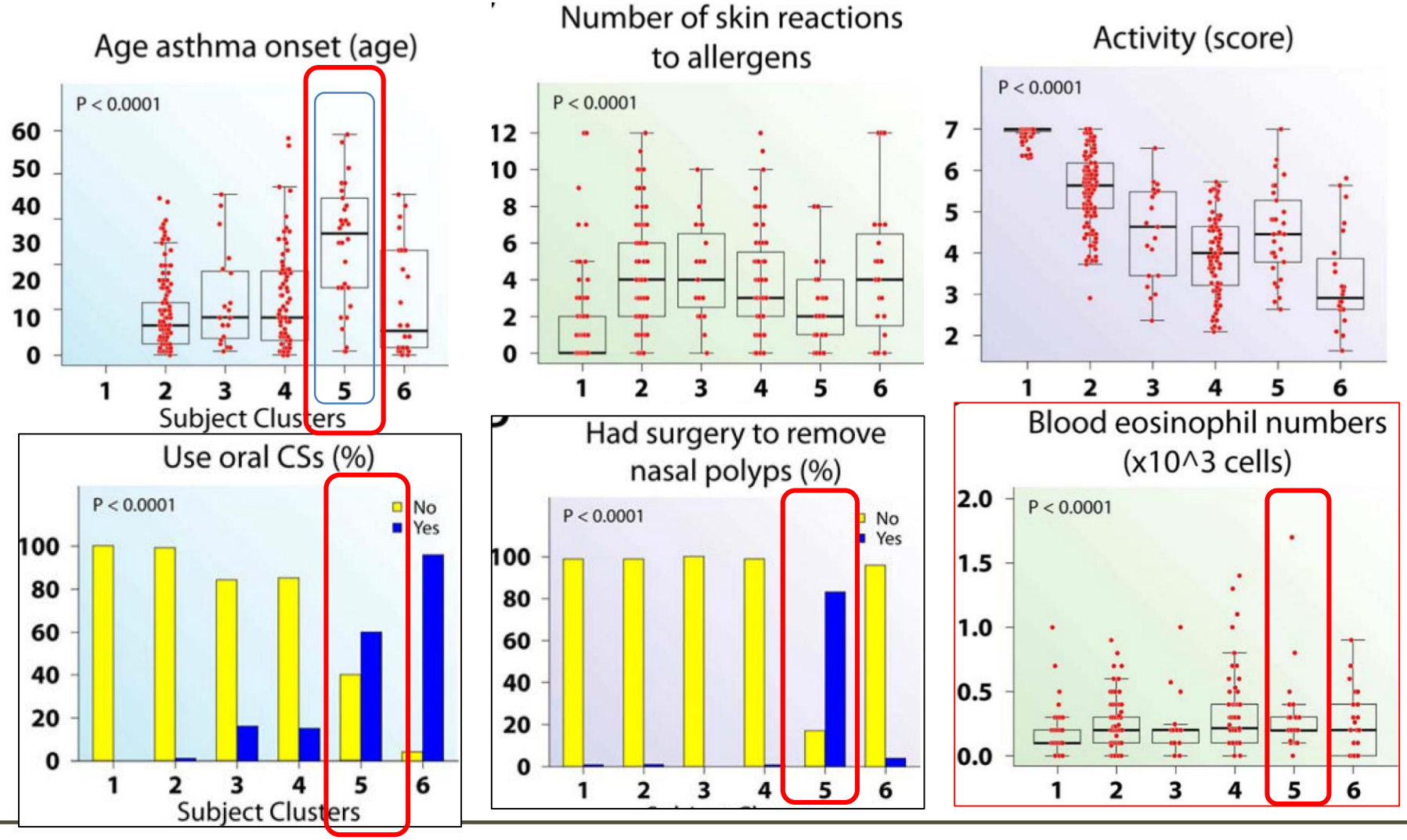
OCS dependent

Frequent AE

Late onset, high Eos and nasal polyps

SARP cluster analysis

Late onset, nasal polyposis, OCS dependent and high eosinophilia

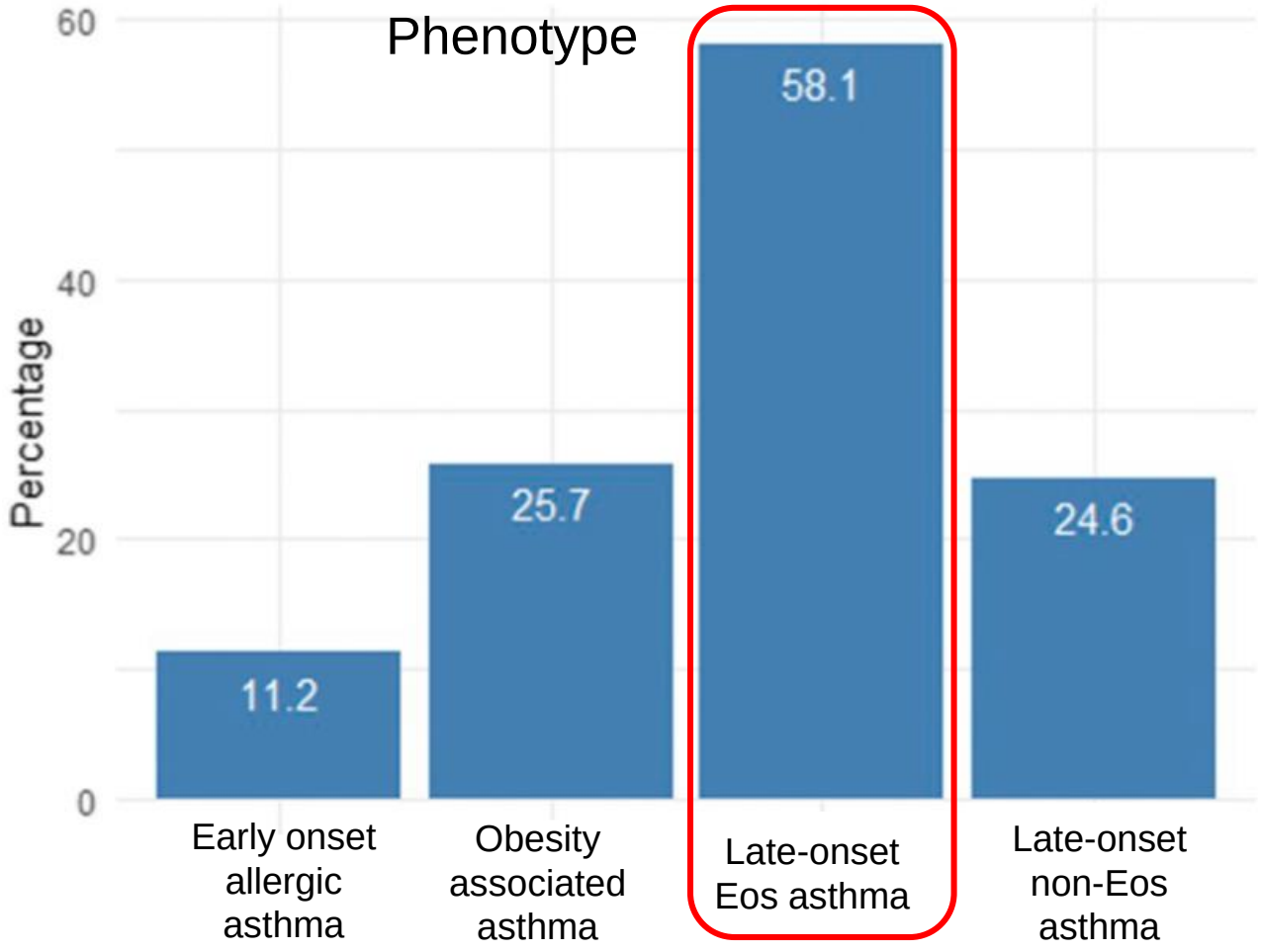


J Allergy Clin Immunol. 2014;133(5):1280-8

Late-onset eosinophilic asthma is the predominant phenotype in severe asthma

Spain, observational, cross-sectional study,

- N=179, 70.8% female
- mean age: 55.3 ± 12.1
- OCS dependent: 21.7%
- Late-onset: age>12 y/o
- Eosinophilic asthma: blood eos>300 cells/µL
- Obesity: BMI ≥ 30 kg/m^2



Respiratory Medicine 2019;151:49–54

Severe allergic asthma vs Severe esosinophilc asthma

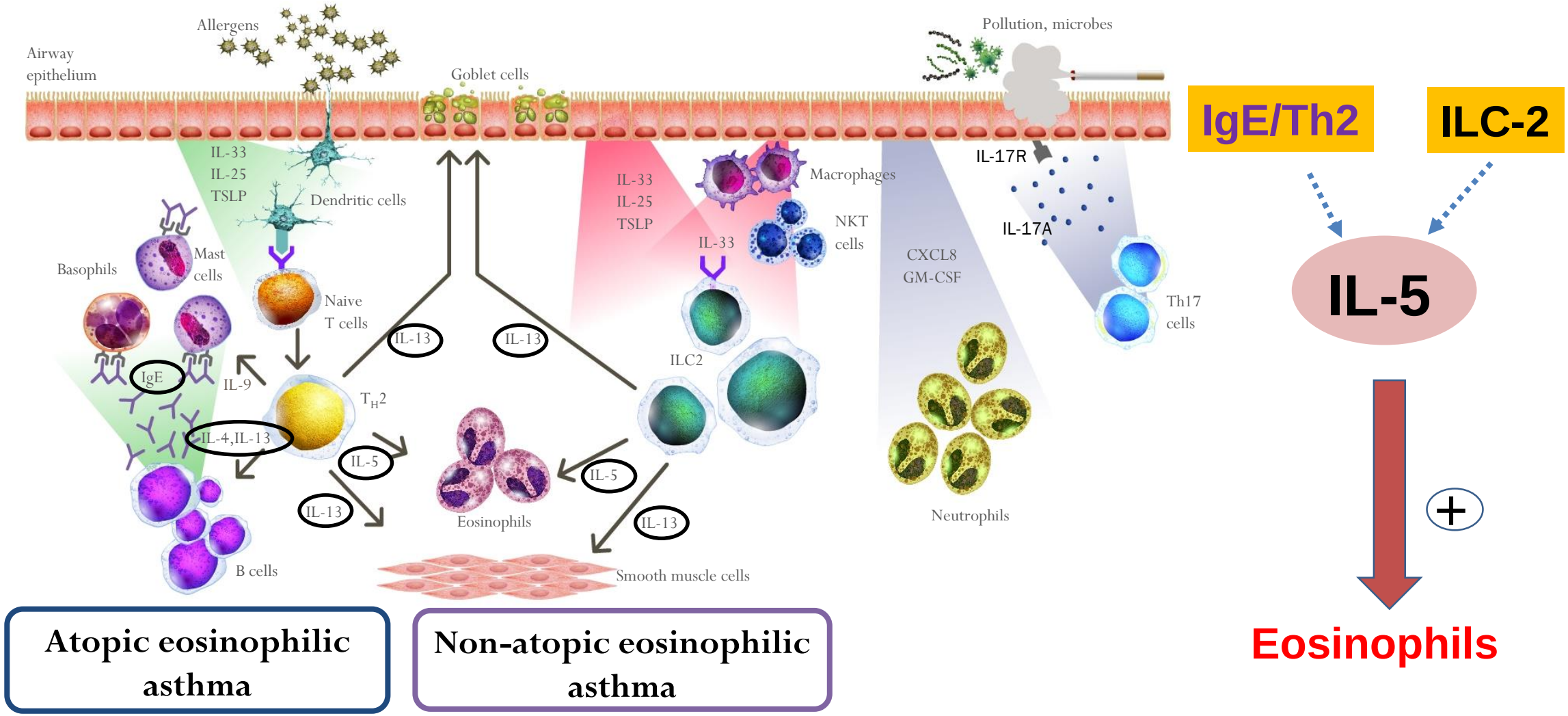
	A: allergic-predominant asthma	B: eosinophilic-predominant asthma
1	Early onset	Late onset
2	SPT/RAST+ with clinically significant allergies#	SPT/RAST– or + with no clinically significant allergies
3	IgE >100 IU·mL^{-1}	IgE <100 IU·mL^{-1}
4	Allergic rhinitis	Nasal polyps
5	High *F*ENO (30–50 ppb)	Very high *F*ENO (>50 ppb)
6	Blood eosinophils <300 cells·µL^{-1}	Blood eosinophils >300 cells·µL^{-1}#

SPT: skin prick test; RAST: radioallergosorbent test; *F*ENO: exhaled nitric oxide fraction. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic- or eosinophilic-predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma. #: obligatory characteristics for allergic and/or eosinophilic asthma.

ERJ Open Res 2018;4:00125-2017

Severe eosinophilic asthma occurred in either atopic or non-atopic pathway

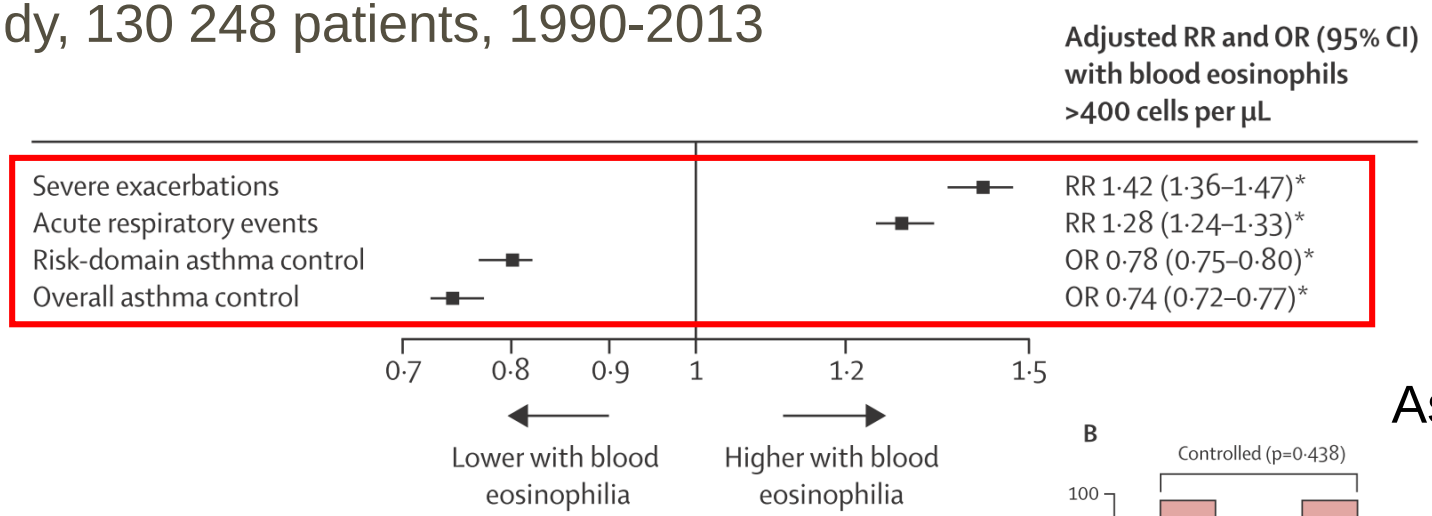
T2 inflammatory pathway

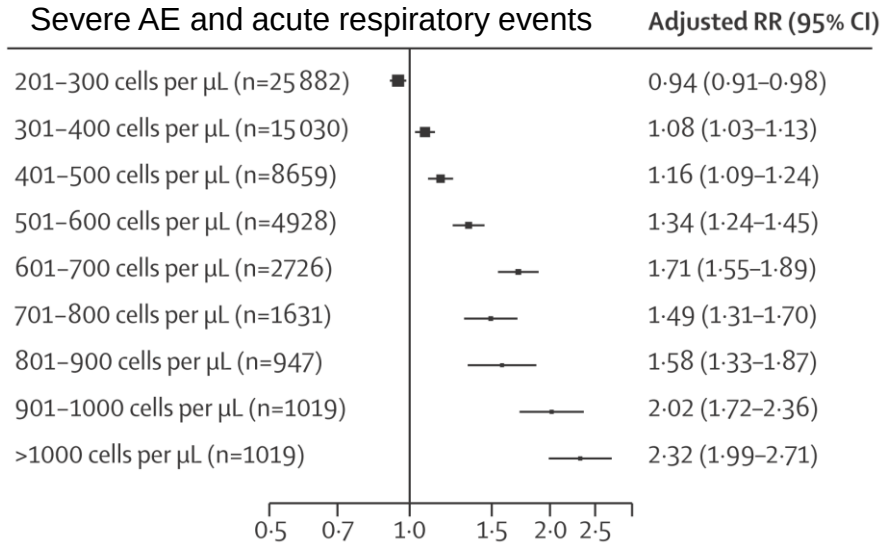


Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

High blood eosinophil counts associated with more acute exacerbation rate and poor asthma control

UK cohort study, 130 248 patients, 1990-2013

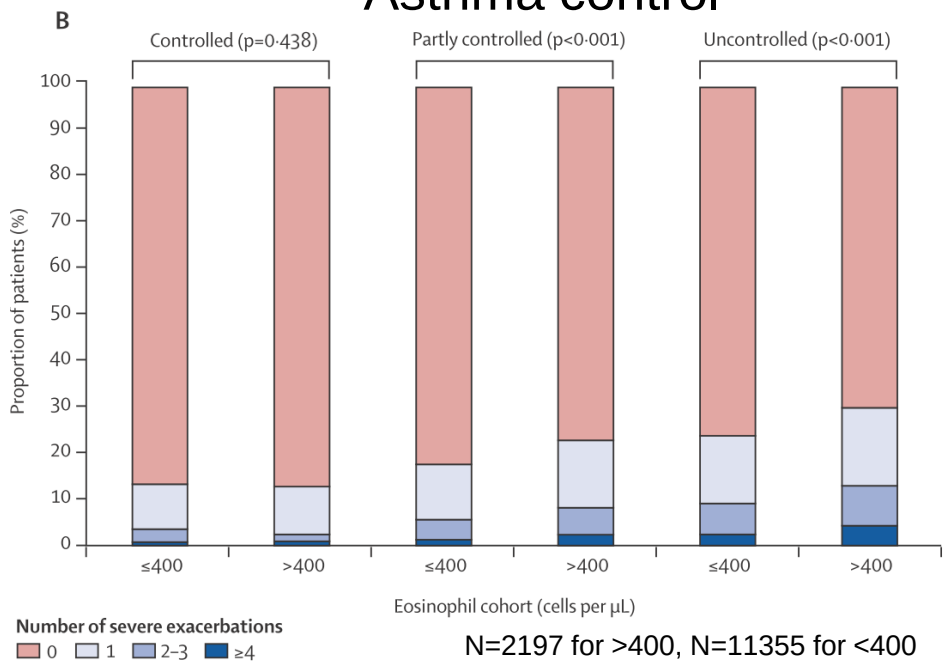




27.6%

EOS>300/ul

Asthma control



N=2197 for >400, N=11355 for <400

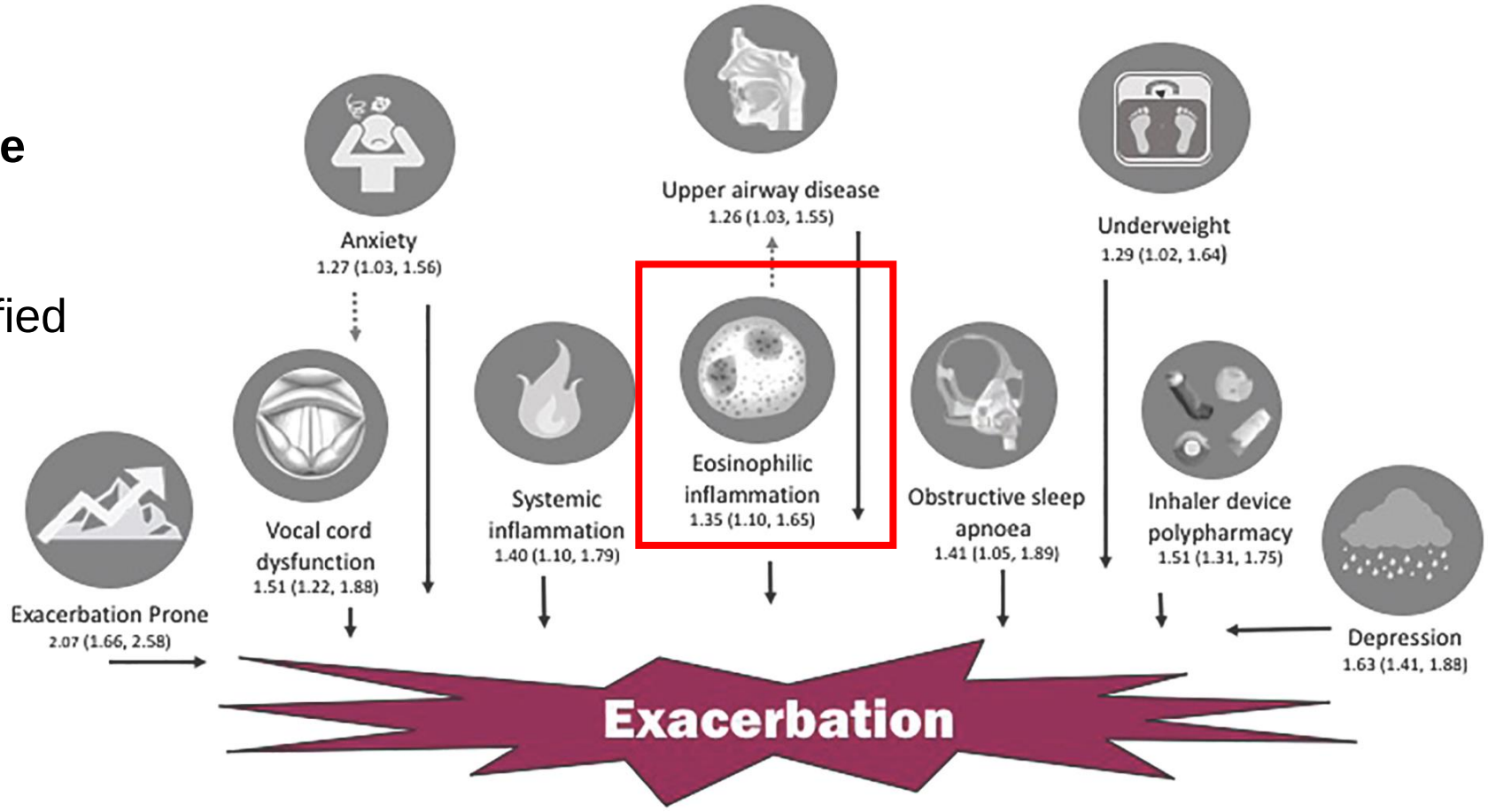
Lancet Respir Med. 2015;3:849-58

Treatable traits can be identified in a severe asthma registry and predict future exacerbations

The Australasian Severe Asthma Web-Based Database (SAWD)

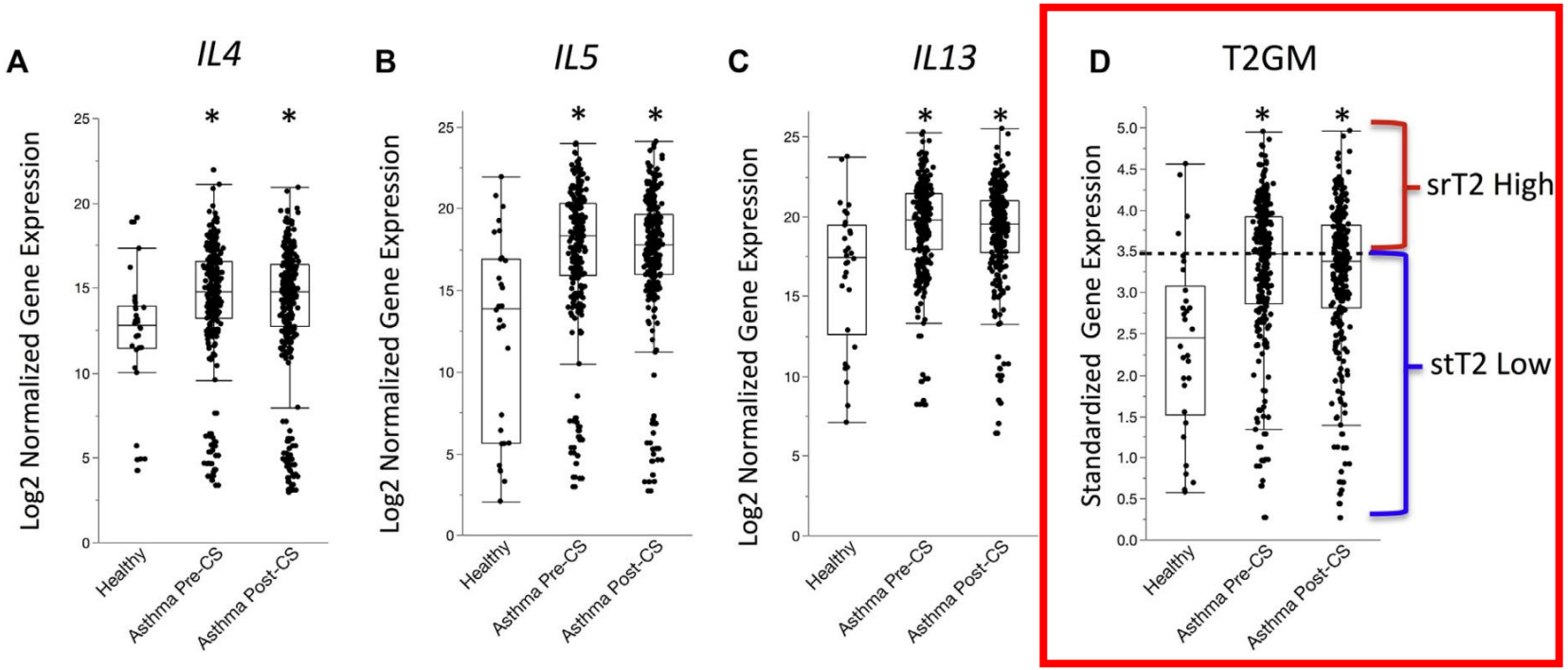
24 treatable traits were identified in 3 domains:

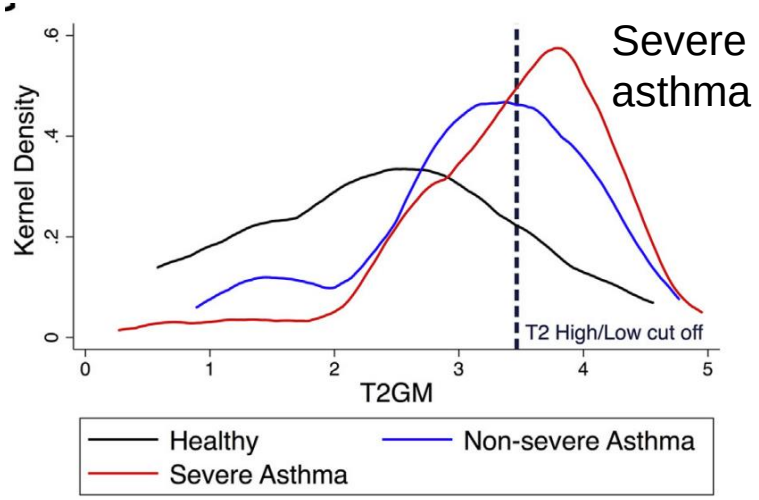
- Pulmonary
- Extrapulmonary
- Behavioural/risk factors.



Respirology 2019;24,37–47

Most of T2 high severe asthma not respond to systemic steroids

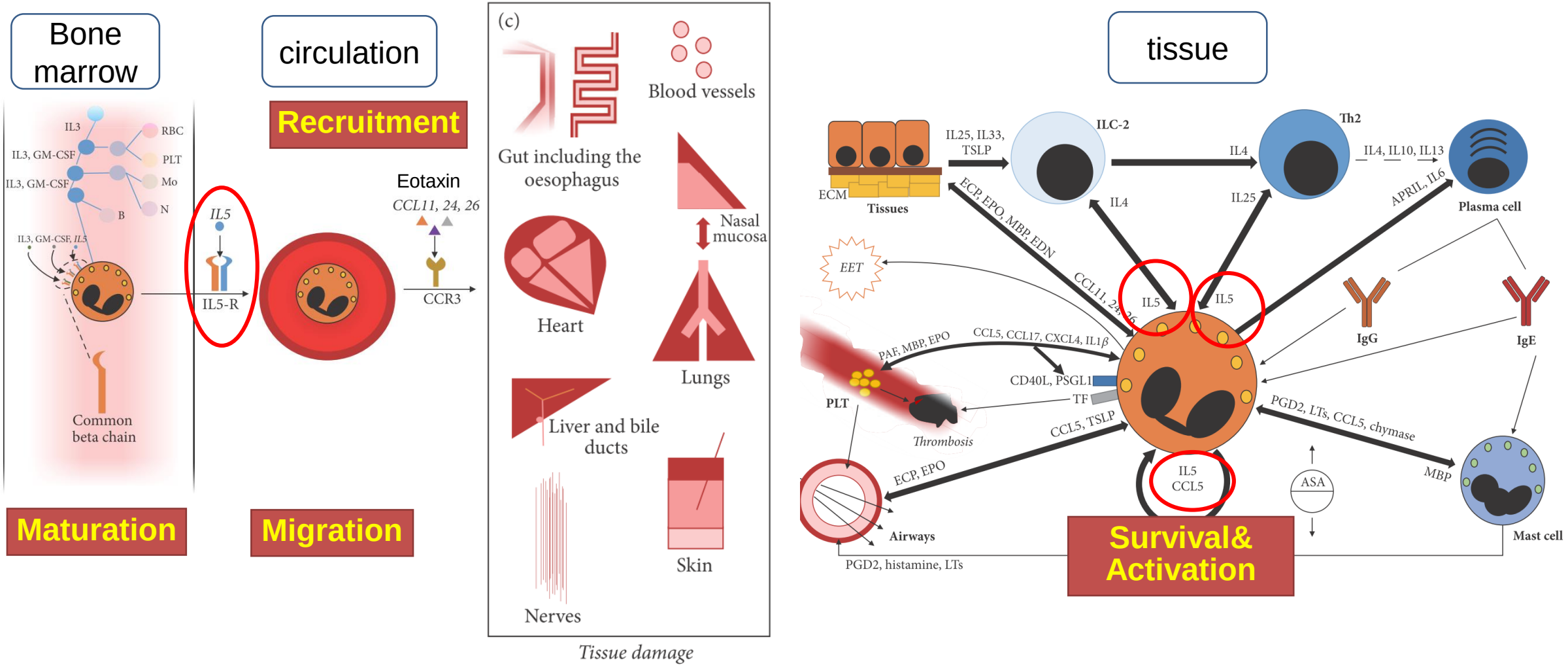




- SARP3 cohort, >60% severe asthma
- Systemic corticosteroids not fully suppress airway type 2 inflammation
- Steroid-resistant T2-high asthma are characterized by more severe disease

JACI 2019;1:104-113

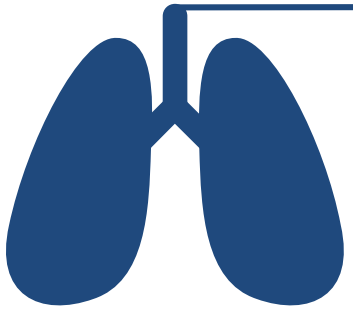
IL-5 is major cytokine related in severe eosinophilic asthma



BioMed Research International 2018; 9095275

Mepolizumab: anti-IL5 monoclonal antibody

Identify the right patients for mepolizumab



Mepolizumab eligibility criteria:[1]

Two or more controller therapies, including high-dose ICS and additional controller(s)

and

Two or more **exacerbations** in the previous 12 months and/or daily OCS

Clinically meaningful response is predicted in patients with blood eosinophil counts of:[2]

≥150 cells/µL at initiation of treatment

or

≥300 cells/µL in the prior 12 months

1.Taiwan Nucala Full PI, USPI201702 2. Ortega HG, et al. *Lancet Respir Med.* 2016;4:549–556.

Mepolizumab demonstrated long-term improvement in asthma control

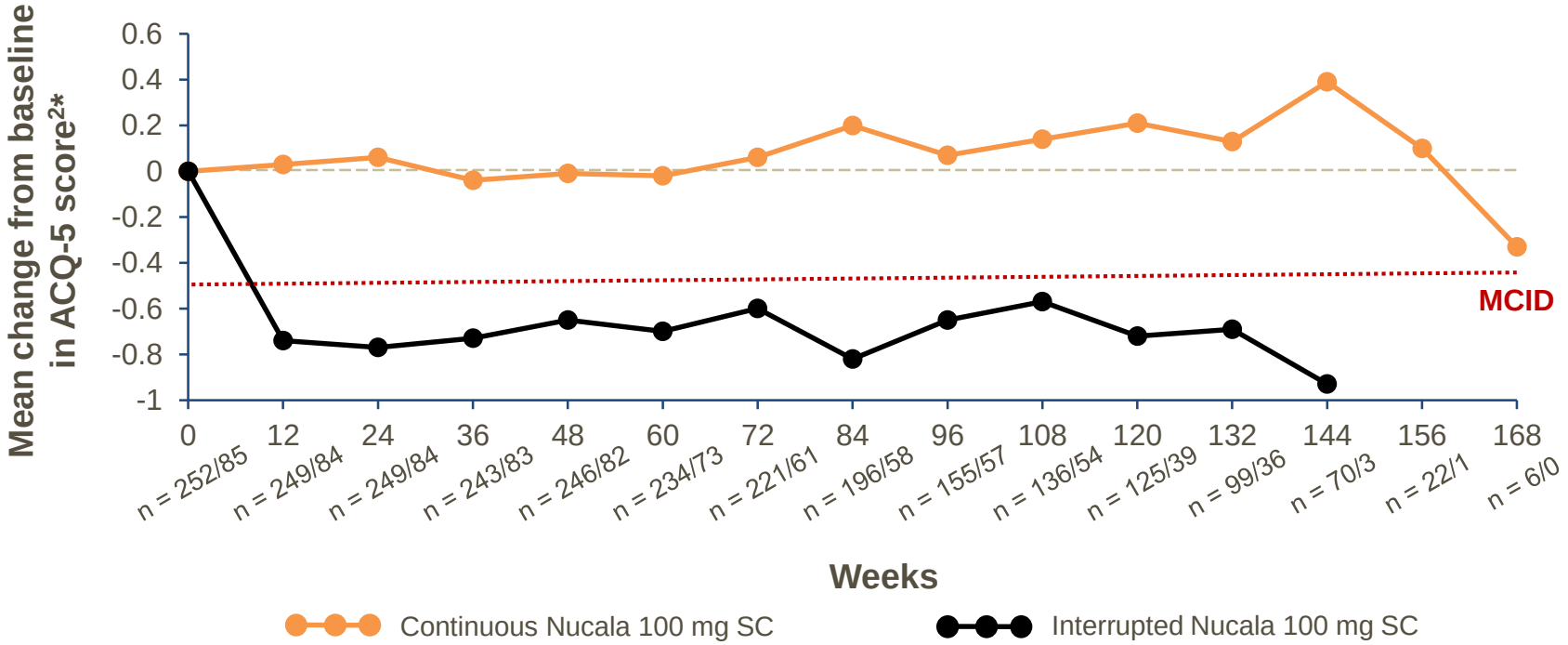
COSMEX study, extension of COSMOS from MENSA and SIRIUS, up to 172 weeks

COSMEX mean baseline ACQ-5 score[1]

Continuous treatment: 1.38

Interrupted treatment: 2.26

(Patients with ACQ scores 0.0–0.75 are well-controlled, 0.75–1.5 are partially-controlled, and >1.5 are uncontrolled)[3]



Continuous treatment defined as ≤12-week gap between last Nucala dose in COSMOS and first dose in COSMEX. Interrupted treatment defined as >12-week gap between last COSMOS dose and first COSMEX dose.
* Data shown for timepoints in which n >1 for each group.
MCID, minimum clinically important difference (reduction of 0.5 points in ACQ-5 score).

1. GlaxoSmithKline. Data on file. REF-21901; 2. GlaxoSmithKline. Data on file. REF-2158; 3. GINA. Global Strategy for Asthma Management and Prevention. 2018. Available from: ginasthma.org [accessed May 2019].

Effectiveness and safety of mepolizumab in real-world clinical practice

REALITI-A study

REALITI-A is an ongoing, 2-year, global, prospective, single-arm, observational cohort study to assess the effectiveness of mepolizumab in patients with SEA in real-world clinical practice

Patient inclusion criteria

- Adults with SEA
- Newly prescribed mepolizumab at physician's discretion
- ≥12 months of medical record data available prior to enrolment

Primary outcome

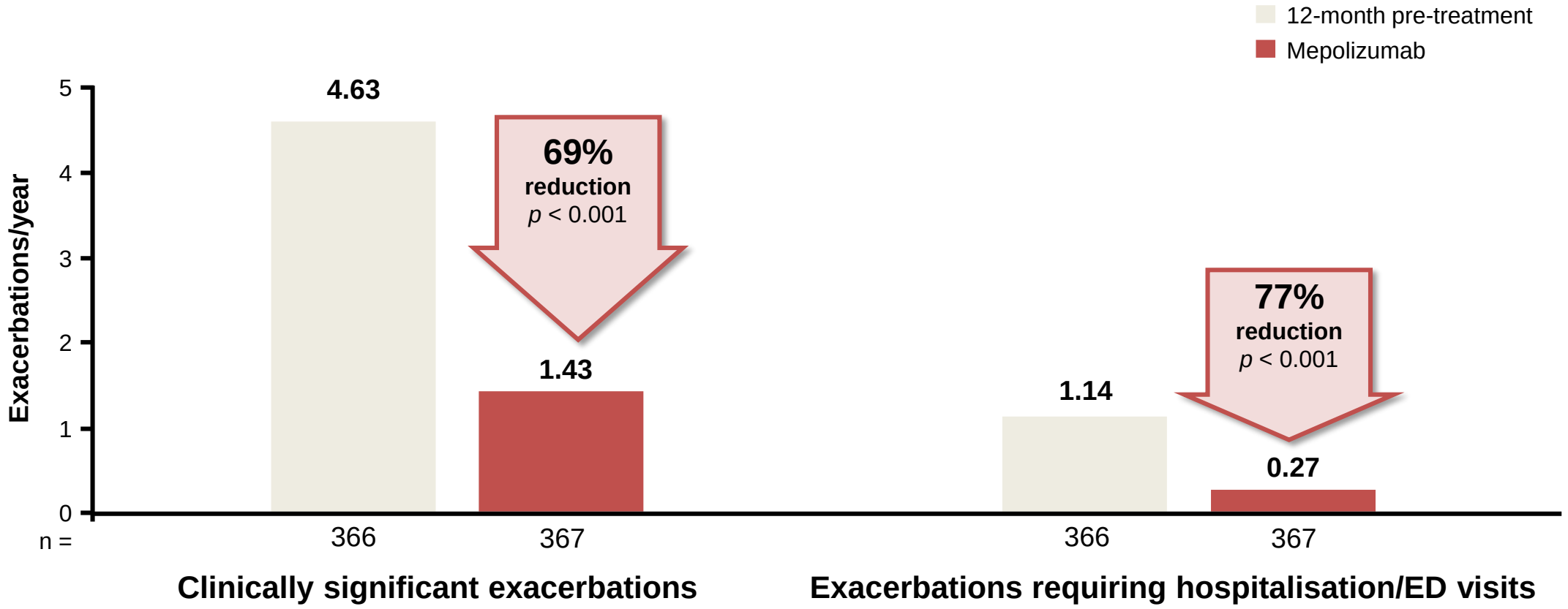
- Rate of clinically significant exacerbations at 12 months post-exposure*

SEA, severe eosinophilic asthma.
* Compared with 12 months prior to mepolizumab exposure; clinically significant exacerbations defined as those requiring ED visit / hospitalisation and/or use/increased dose of OCS therapy

1. Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104;2. GlaxoSmithKline. 204710-A multinational, single-arm, observational study to evaluate the real-world effectiveness and pattern of use of mepolizumab in patients with severe eosinophilic asthma (204710: the REALITI-A study). Available from: gsk-studyregister.com [accessed September 2019].

Mepolizumab reduce the rate of asthma exacerbation in real world

REALITI-A study



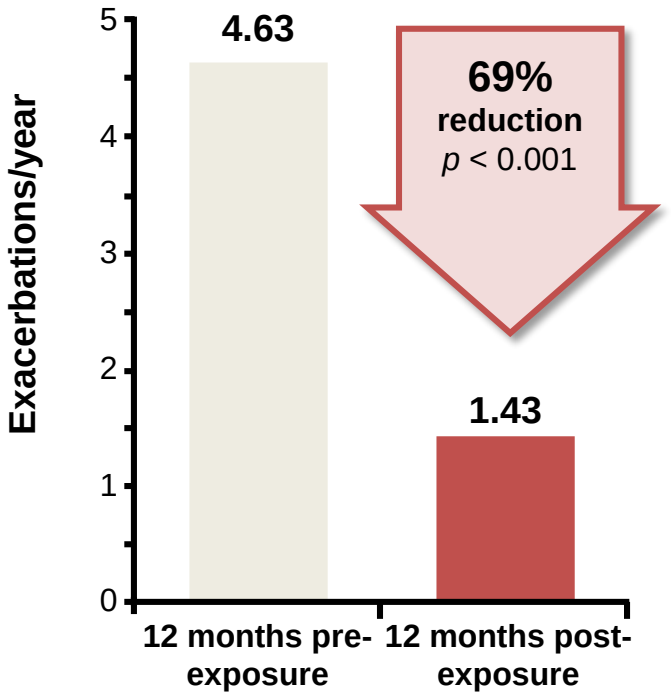
This is an analysis of data from early initiators in the REALITI-A study, with 12 months of post-exposure data available..

Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104

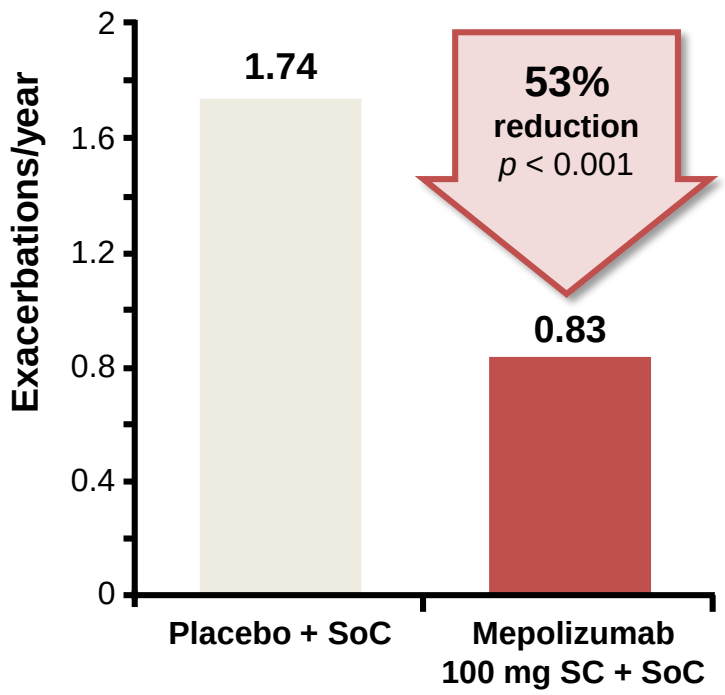
REALITI-A study and clinical trials

Reduction in asthma exacerbation

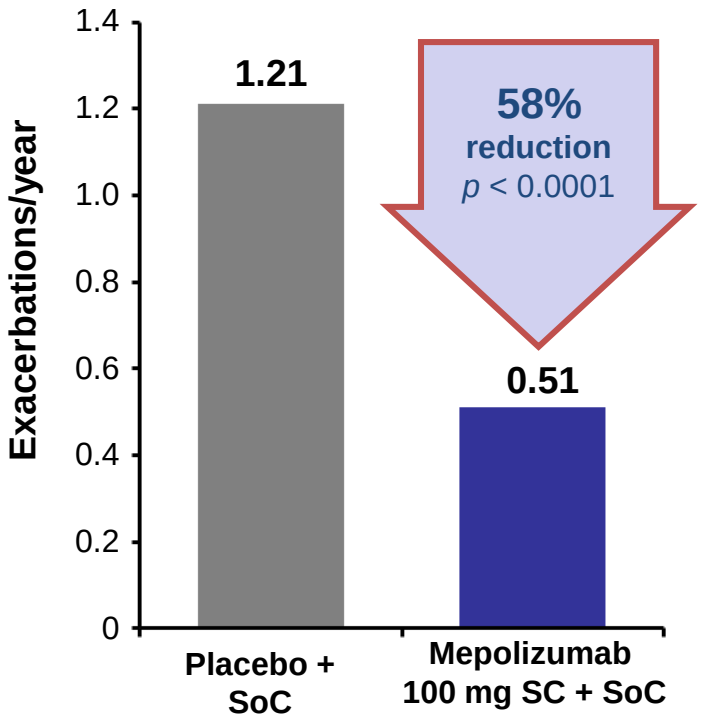
REALITI-A[1]



MENSA[2]



MUSCA[3]



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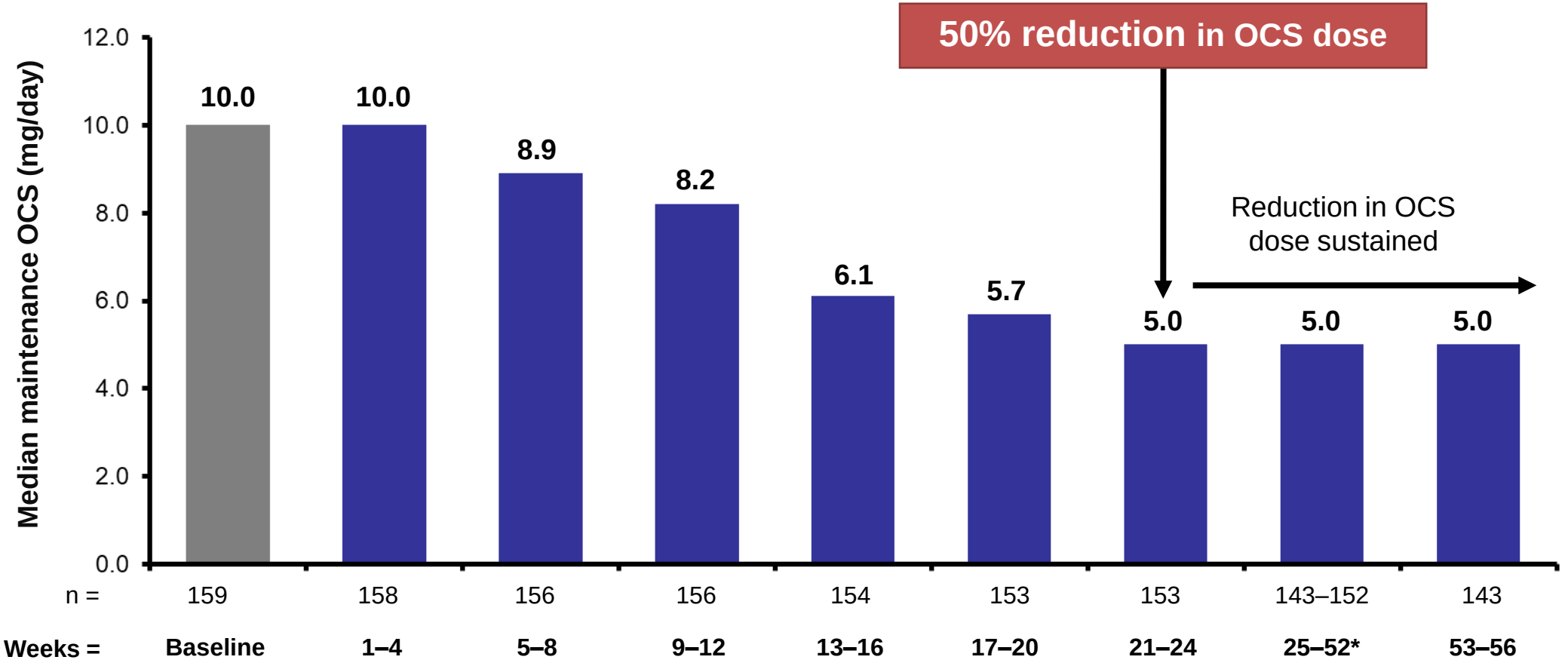
1. Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104;
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207;
3. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3b trial. *Lancet Respir Med.* 2017;5:390–400.

Mepolizumab reduce OCS use in real world setting

REALITI-A study



This is an analysis of data from early initiators in the REALITI-A study, with 12 months of post-exposure data available.

* Median OCS remained at 5.0 mg/day for all assessment time periods from weeks 25 to 52.

Adapted from Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104.

Safety

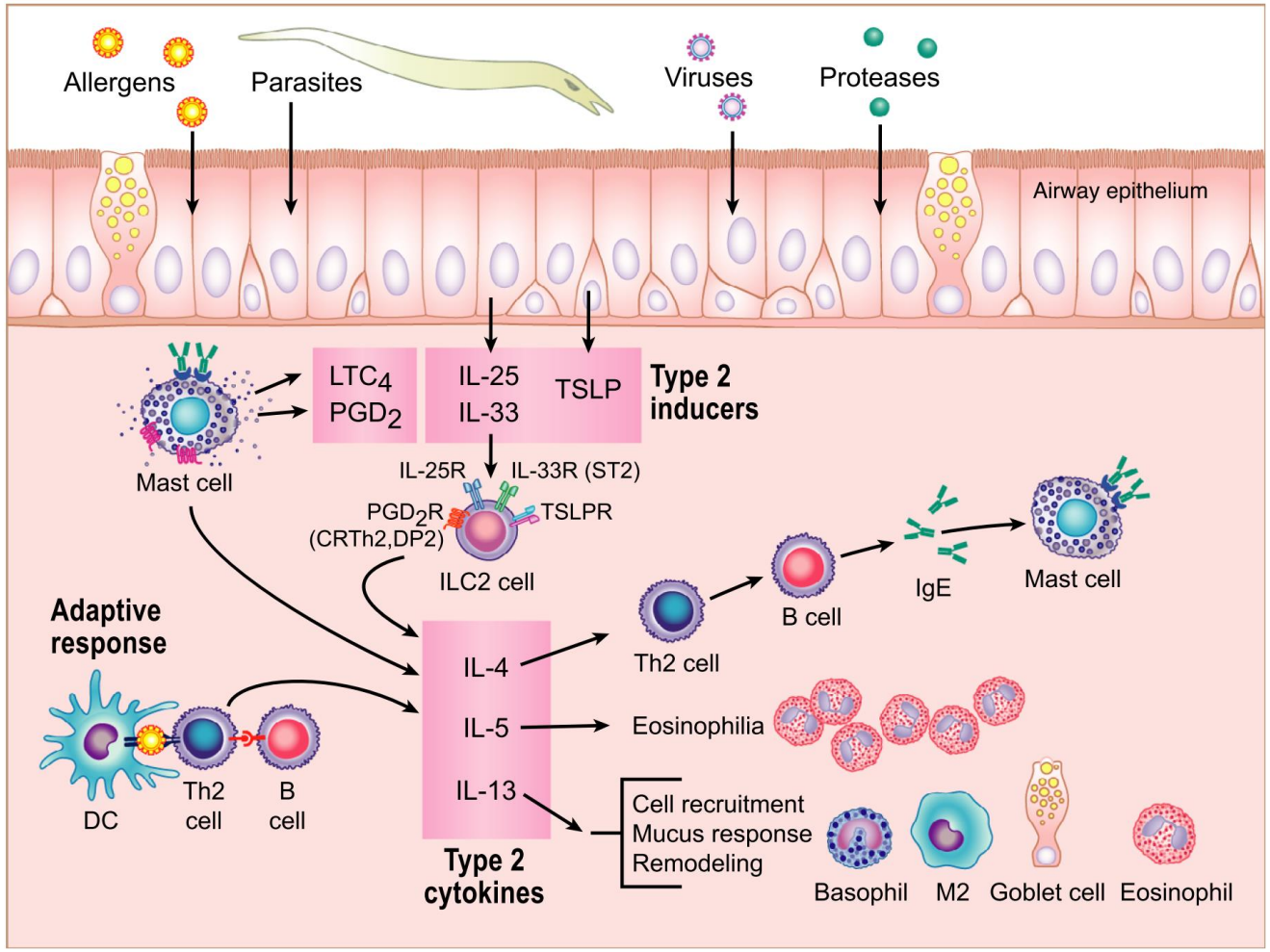
REALITI-A study

Event, n (%)	Mepolizumab 100 mg SC (N = 368)
Any on-treatment AEs	53 (14)
AE related to study treatment leading to permanent discontinuation	9 (2)
Any on-treatment SAE	2 (<1)
Related to study treatment	2 (<1)
Fatal	0

This is an analysis of data from early initiators in the REALITI-A study, with 12 months of post-exposure data available.

Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104.

Nasal polyps correlate with chronic T2 inflammation



- ***Chronic inflammation***, rather than atopic allergy induced
- Predominant T2 inflammation **by ILC2 cells**
- 80% to 90% of the nasal polyps are characterized by prominent eosinophilia

Clinical & Experimental Allergy 2014;45,328–346; JACI 2017;140:1024-31; J Allergy Clin Immunol 2011;128:989-95

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** for severe allergic asthma?*

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no ↓ ↑ *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no ↓ ↑ *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

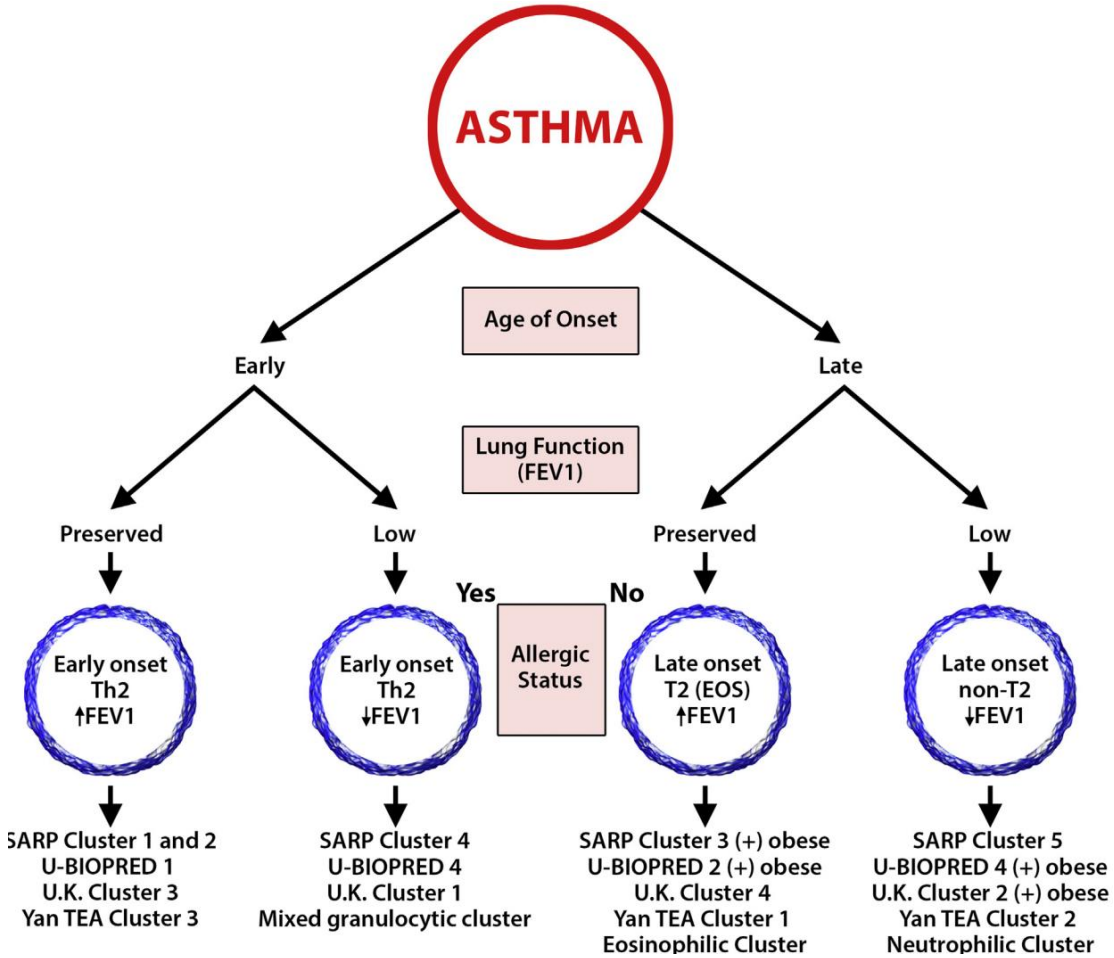
Anti-IL4R may also be used to treat

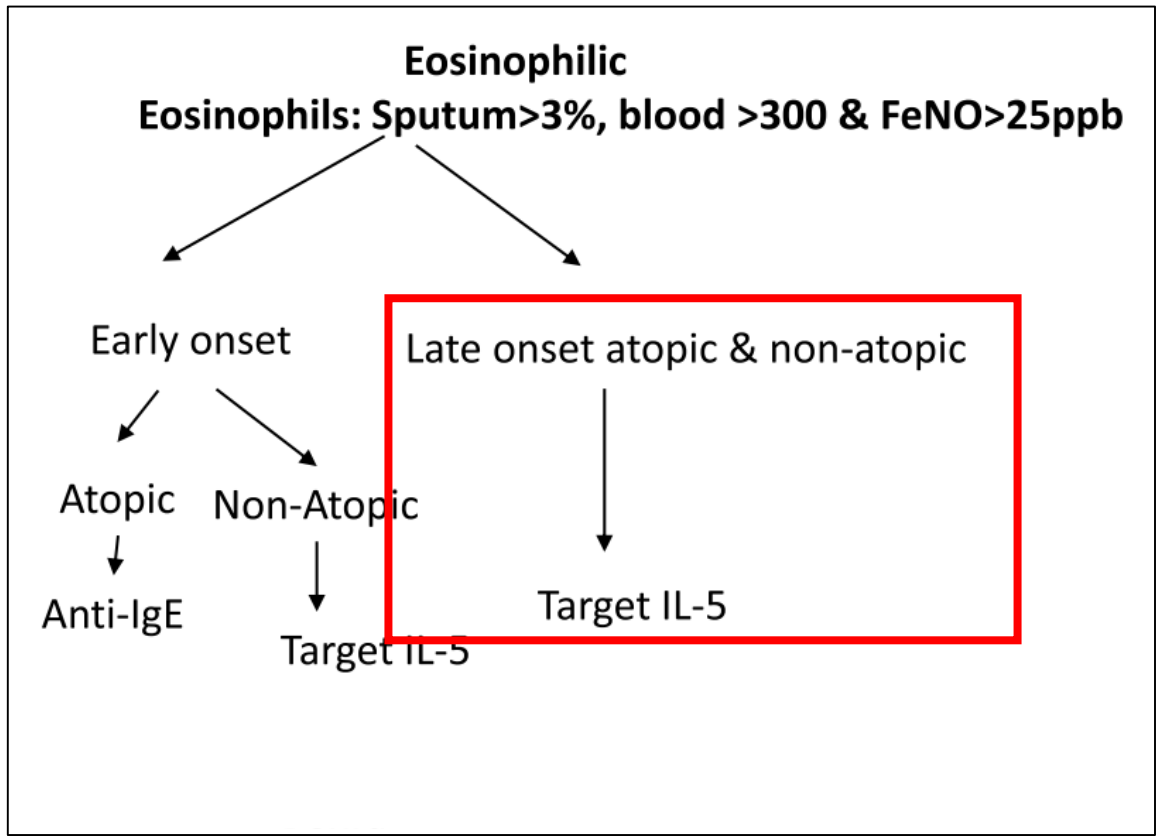
- Moderate/severe atopic dermatitis
- Nasal polyposis

Choose one if eligible; trial for at least 4 months and assess response

GINA Guidelines, 2019

Proposed treatment algorithm for severe eosinophilic asthma





J Allergy Clin Immunol 2019;144:1-12
Respiratory Medicine 2018;142:15–22

Integrated Safety Information

Adverse reactions with mepolizumab 100 mg SC with ≥3% incidence and more common than placebo in MENSA and SIRIUS studies.

Adverse Reaction	Mepolizumab 100 mg SC (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo.

Taiwan Nucala Full PI, USPI201702

英文產品名稱：NUCALA Powder for Solution for Injection (Mepolizumab)
衛部菌疫輸字第001015號

中文產品名稱：舒肺樂凍晶注射劑

成分含量：注射劑，100毫克冷凍乾燥粉末，單劑小瓶裝，須泡製使用。

適應症與用途：表現型為嗜伊紅性白血球的嚴重氣喘且控制不良（severe refractory eosinophilic asthma）之成人患者之附加維持治療。

用法用量：NUCALA的建議劑量為每4週一次於上臂、大腿或腹部皮下注射100毫克。

禁忌症：NUCALA不可用於曾對mepolizumab或配方中之賦形劑產生過敏反應的患者。

警語和注意事項
過敏反應：
曾有在投予NUCALA之後發生過敏反應（如血管性水腫、支氣管痙攣、低血壓、蕁麻疹、皮疹）的報告。這些反應通常都是在投藥後數小時內發生，但有些病例會延遲發生（即數日後才發生）。如果發生過敏反應，應停用NUCALA。
急性氣喘症狀或惡化性疾病：
NUCALA不可用於治療急性氣喘症狀或急性惡化。切勿使用NUCALA治療急性支氣管痙攣或氣喘重積狀態。在開始使用NUCALA治療之後，如果患者的氣喘症狀仍未獲得控制或出現惡化的現象，應尋求醫療建議。
伺機性感染：帶狀皰疹
在對照性臨床試驗中，使用NUCALA治療的受試者有2個發生帶狀皰疹的嚴重不良反應病例，安慰劑組則無任何此類病例。在開始使用NUCALA治療之前，如果醫療條件適合，應考慮接種水痘疫苗。
降低皮質類固醇的劑量：
開始使用NUCALA治療時，切勿驟然停用全身性或吸入性皮質類固醇。如果適合降低皮質類固醇的劑量，應以逐步漸進的方式降低劑量，並應在醫師的直接監督之下進行。降低皮質類固醇的劑量可能會引發全身性戒斷症狀，並或使先前被全身性皮質類固醇壓制的症狀顯露出來。
寄生蟲（蠕蟲）感染：
嗜伊紅性白血球可能會涉及某些蠕蟲感染所引發的免疫反應。已知患有寄生蟲感染症的患者都被排除於臨床試驗之外。目前並不確知NUCALA是否會影響患者對寄生蟲感染的反應。對原先即患有蠕蟲感染症的患者，在開始使用NUCALA治療前應先治療其感染症。如果患者在接受NUCALA治療期間發生感染，並且對抗蠕蟲治療無法產生反應，應停止使用NUCALA治療，直到感染消退。

常見不良反應：頭痛、注射部位反應、背痛、疲倦等。

•不良事件通報程序：通報電話:（02）23126836/ 郵箱: oax40892@gsk.com
•詳細處方資訊備索

葛蘭素史克藥廠 地址:100台北市忠孝西路一段66號24樓

振興醫療財團法人
振興醫院

Thank you for your listening

ponda0294@gmail.com