Management of Severe Asthma

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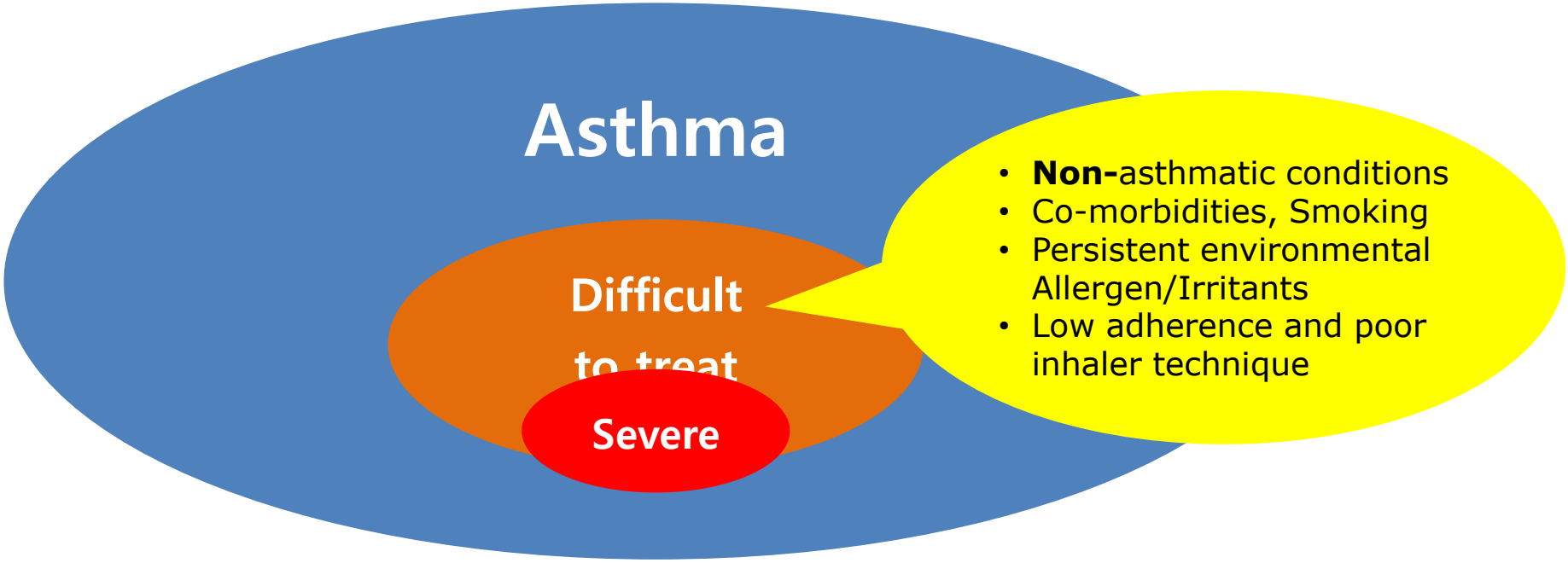
Severe Asthma



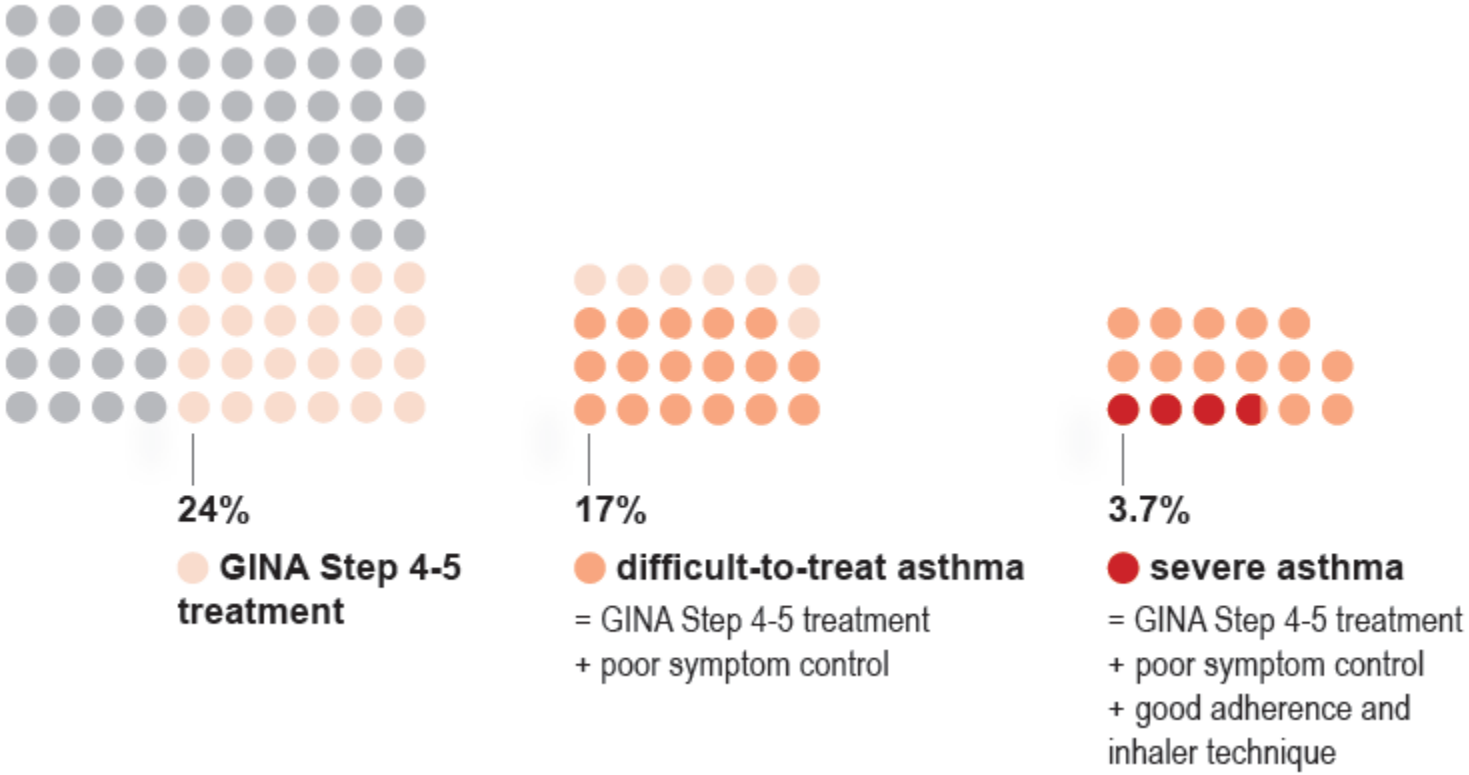
고용량의 흡입스테로이드와 2차 조절제 또는 경구 스테로이드/생물학적 제제를 사용해야 조절상태에 도달하거나 그럼에도 조절되지 않는 천식

조절되지 않는 천식의 정의는 다음 중 하나에 해당한다.

1) 낮은 증상 조절: 한국 천식 진료 지침의 부분조절 상태, 또는 천식 조절 검사에서 20점 미만
2) 잦은 천식 악화: 전신 스테로이드가 3일 이상 필요한 정도의 천식 악화가 연 2회 이상
3) 중증 악화: 천식 악화로 입원이나 기계호흡이 필요한 경우
4) 기류제한: 기관지확장제 사용 후 FEV1 < 80%

천식진료지침 2014
김주희. 대한내과학회지 2018:93(2) ;153
Chung KF, et al. ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.

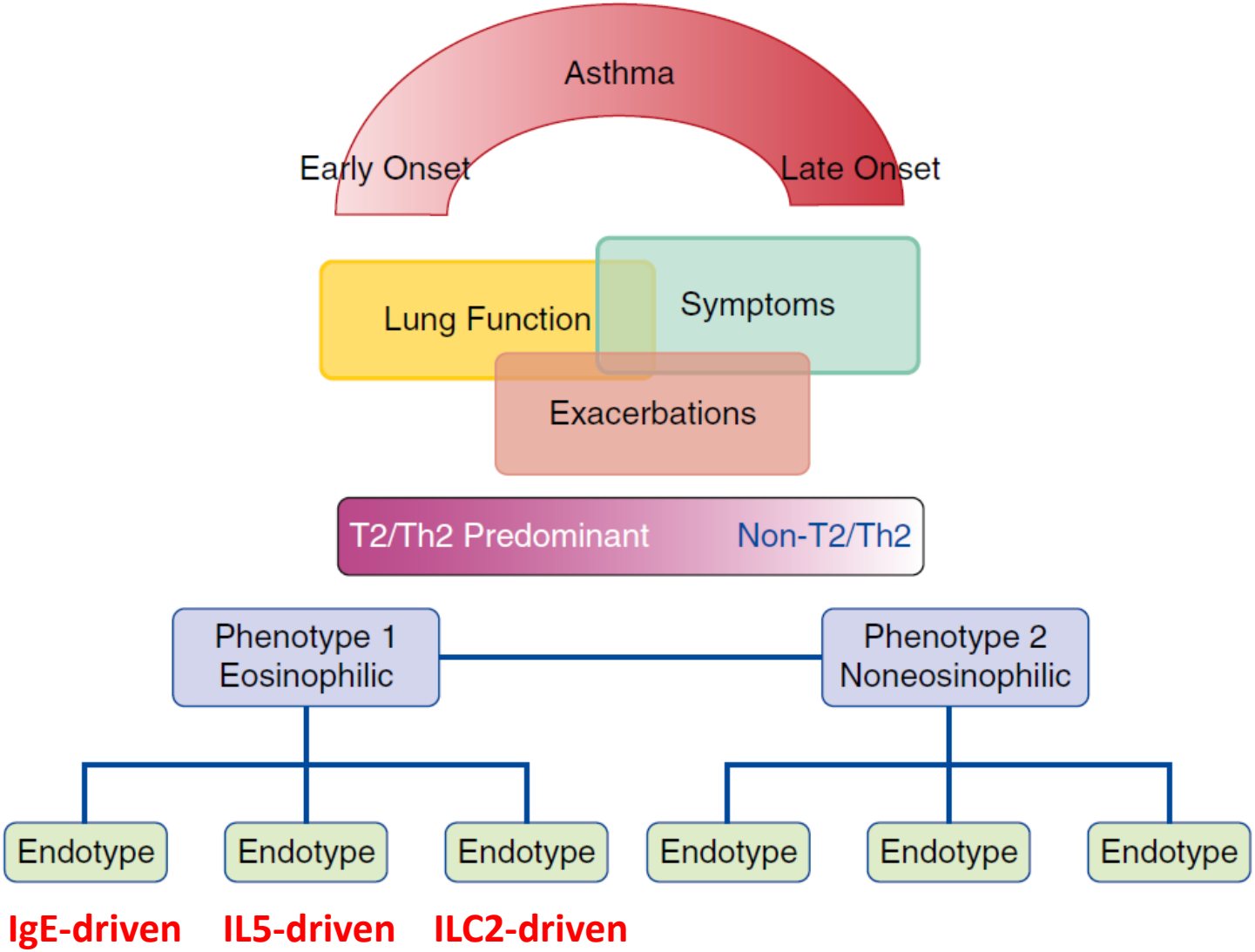
What proportion of adults have difficult-to-treat or severe asthma?



- Data from a Dutch population survey of people ≥18 years with asthma

Hekking PP, et al, The prevalence of severe refractory asthma. J Allergy Clin Immunol, 2015;135:896-902

Targeted therapy for severe asthma based on phenotype and endotype



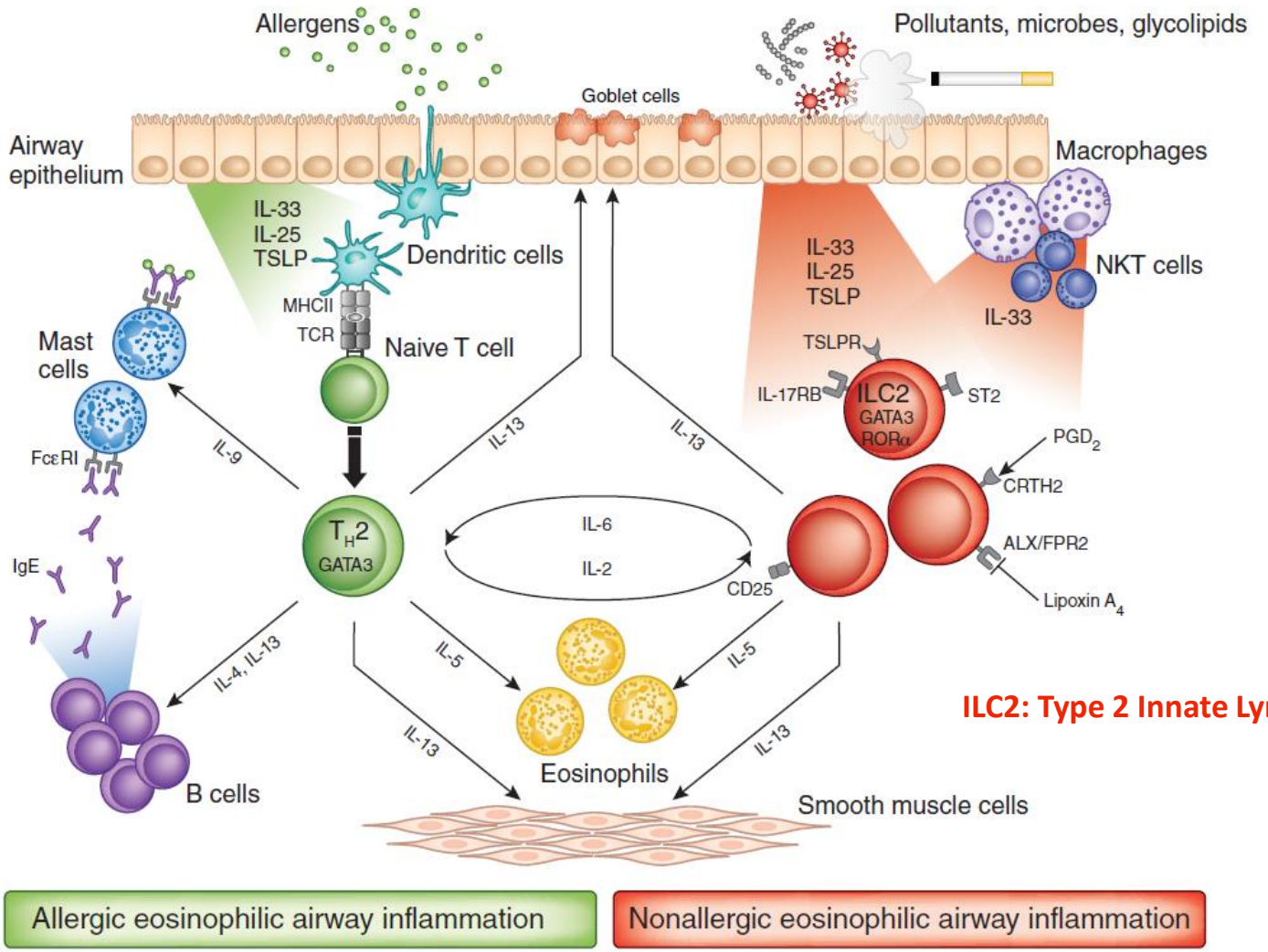
Carr et al. Am J Respir Crit Care Med 2018: 197(1);22–37

Allergic vs Non-allergic asthma phenotype

	Allergic (Extrinsic)	Non-allergic (Intrinsic)
Age at asthma onset	Younger	Older
Allergic trigger	Yes	No
Seasonal symptom pattern	Marked	Not marked
Nasal polyps	Less common	More common
Disease Severity	Less	More
Current or family history of atopy/eczema	More common	Less common

Rackemann, F. A working classification of asthma. Am. J. Med. 1947: 3; 601–606

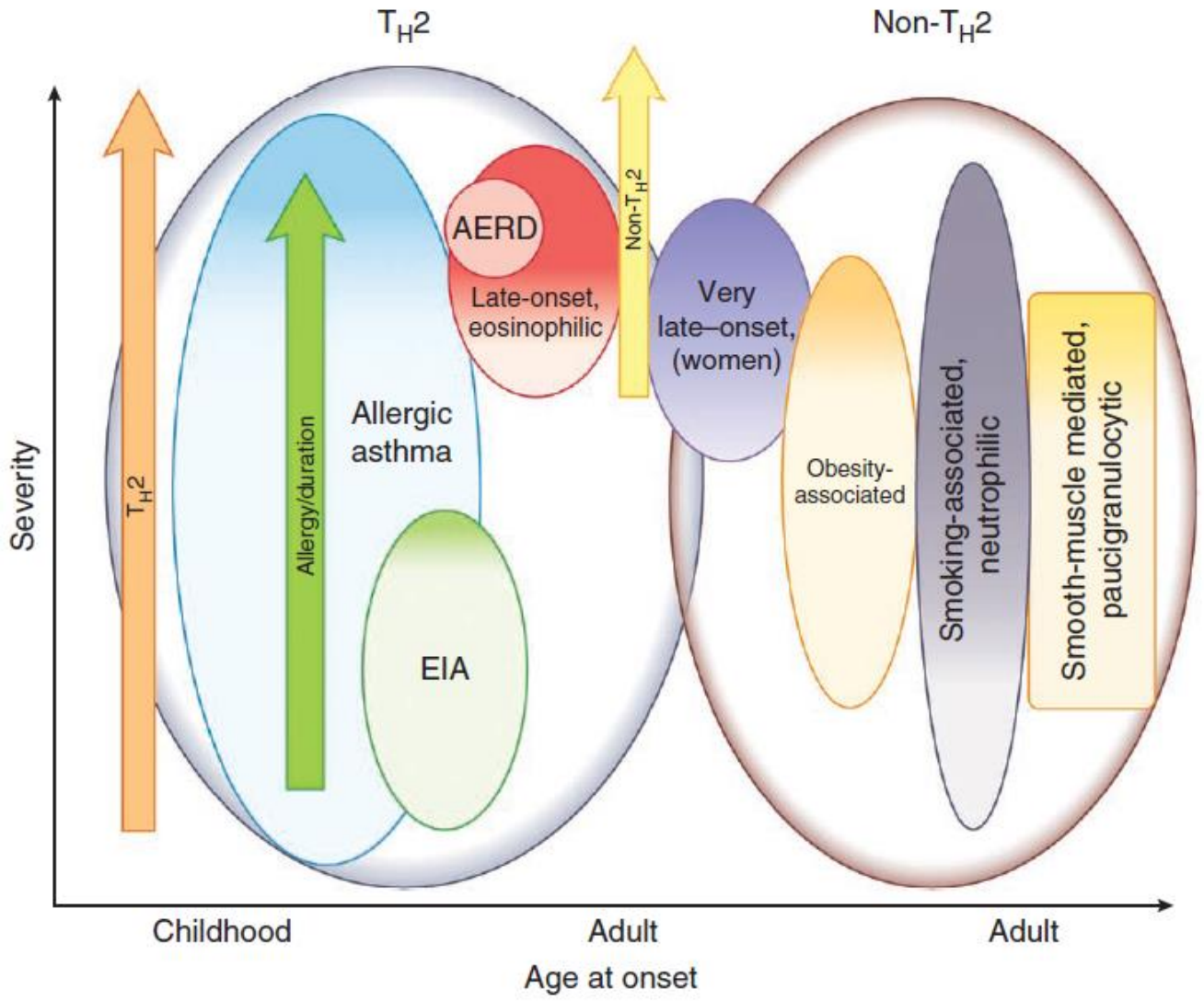
Eosinophilic airway inflammation in non-allergic asthma



ILC2: Type 2 Innate Lymphoid Cells

Brusselle GG et al. Nat Med. 2013;19(8):977-9

Asthma Heterogeneity across age and severity



Wenzel et al. Nat Med. 2012;18(5):716-25.

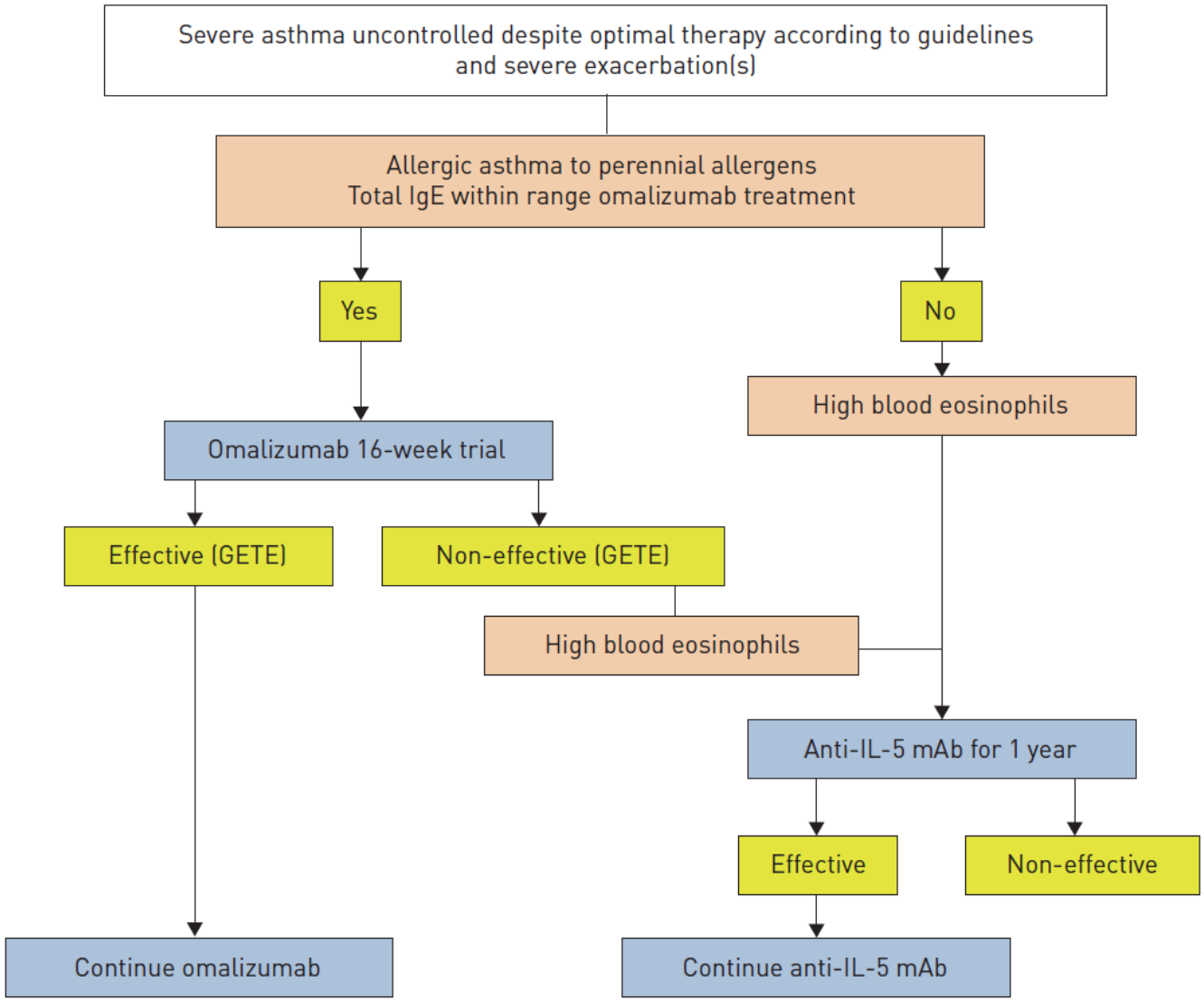
Asthma Phenotypes with Type 2 Signatures

	Age at Onset	Corticosteroid Responsiveness	IgE/Atopy	Cellular Inflammation	Additional Characteristics
Mild–moderate allergic asthma	Childhood	Good to excellent	High	Low level, corticosteroid-responsive eosinophilia	Seasonal allergic symptoms
Severe allergic asthma	Childhood	Modest to poor	High	Low level, less corticosteroid-responsive eosinophilia and neutrophiliia	Fewer allergic symptoms
Highly eosinophilic (blood), despite ICS	30–40 yrs of age	Typically requires (but responds to) systemic corticosteroids	Generally low	Persistent high eosinophilia possible ILC2 involvement	Nasal polyps, sinusitis, aspirin sensitivity
Type 2 plus additional immune pathways (type 1, 17, etc.)	Middle age	Poor	Low	Persistent eosinophils	Systemic connective tissue symptoms, familial autoimmunity

Definition of abbreviations: ICS, inhaled corticosteroids; ILC2, innate lymphoid cell type 2.

Sally E. Wenzel. Am J Respir Cell Mol Biol 2016; 55(1):1–4

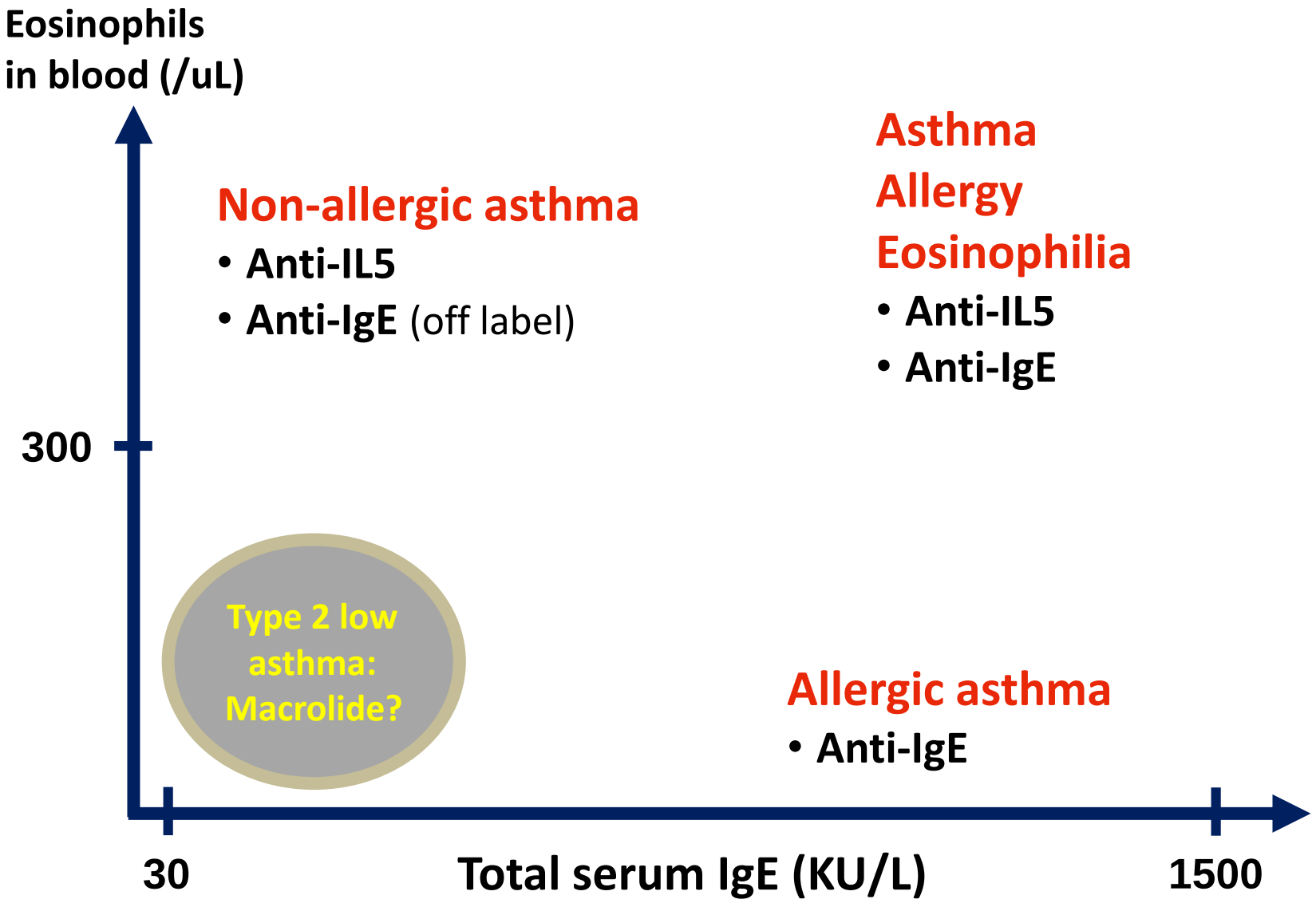
Care pathways for biologics in severe asthma



Eur Respir J 2017;50:1701782

Biologics for severe asthma

Roland Buhl et al. Eur Respir J 2017



Eosinophilic asthma 가능성 높은 환자는?

1. 45세 남성 흡연자 – late onset asthma, bronchitis
2. 56세 비흡연 여성 – adult onset asthma, obesity and GERD
3. 32세 여성 – asthma, nasal polyps and aspirin sensitivity
4. 63세 비흡연 여성 – late onset asthma, fixed AF obstruction

증례

60세 남자

Dyspnea

Remote onset> 10 years ago

History

- 5년 전 Ex-smoker (30 pyrs)
- 10년 전 부터 호흡곤란과 가슴 답답함이 발생하여 ACO 진단 받은 후 ICS/LABA, LAMA, montelukast, theophylline, azithromycin, roflumilast, 경구 스테로이드 사용 중이나 증상 악화 반복되어 응급실 방문 및 입원을 반복
- 냄새를 못 맡는다. 만성 비염/부비동염 + on nasal anti-histamine/steroid

Eexamination & Medication

- 청진상 expiratory wheezing

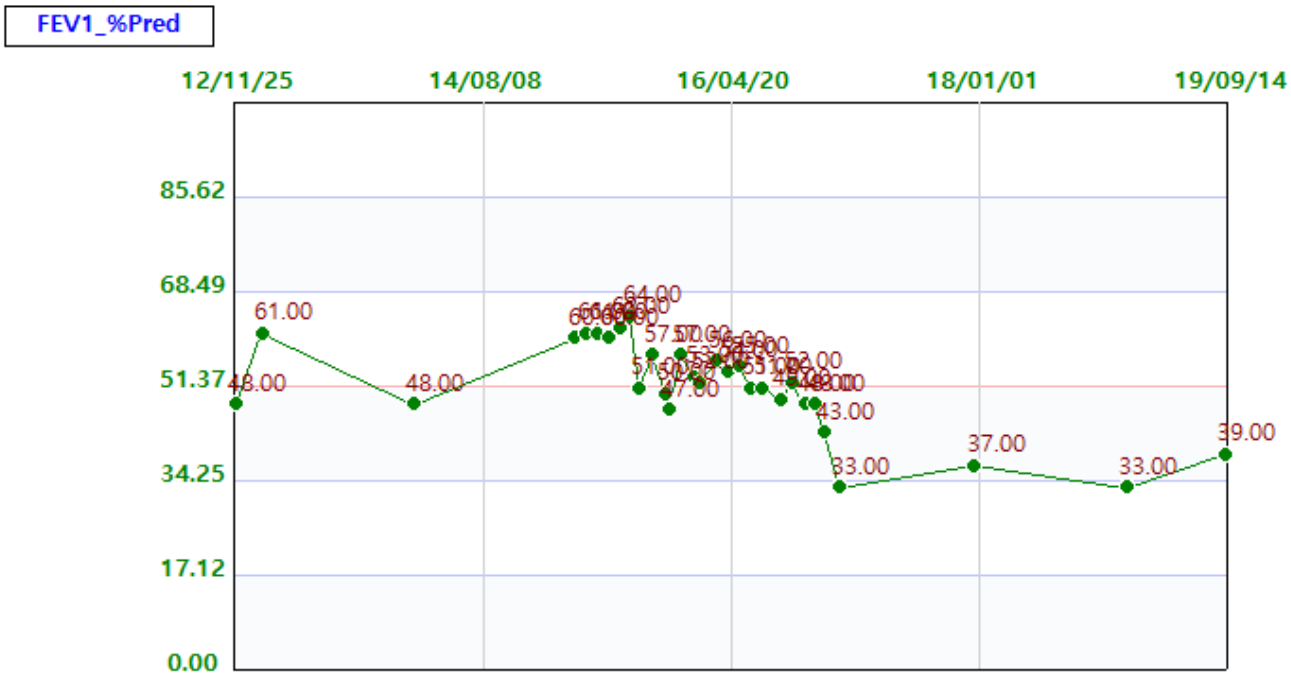
- Ventoline prn (하루 10회 이상 사용), Atrovent nebulizer

Investigation

- Initial lab: eosinophil 0%, IgE 55 MAST: all negative
- Sputum eosinophil: 0%

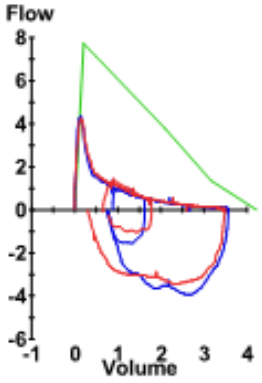
검사코드	검사항목	단위	상한치	하한치	검사일자 2018-08-21	검사일자 2018-05-24	검사일자 2015-12-16	검사일자 2015-09-04	검사일자 2014-07-24
L21262	Polysegmented neutrophil		0	0	86.0		45.0	69	74%
L23261	Eosinophil stain (sputum		0	0	0	0	0	0	4%

- PFT

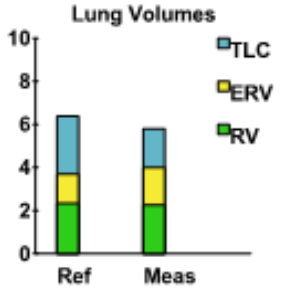


Gender: Male	Room: Pulm		Date: 09/09/19
Age: 60	Race: Asian		Physician: 나승원
Height(cm): 168	Weight(kg): 45.0		Technician: 이민수
Any Info: EX.30PY			

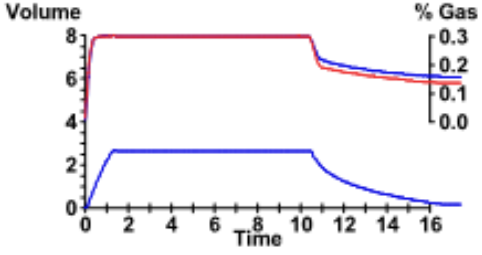
		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	4.23	3.57	84	3.49	82	-2
FEV1	Liters	3.38	1.31	39	1.39	41	6
FEV1/FVC	%	75	37		40		
FEF25-75%	L/sec	2.92	0.39	13	0.46	16	17
IsoFEF25-75	L/sec	2.92	0.39	13	0.55	19	39
PEF	L/sec	7.69	4.36	57	4.22	55	-3
PEFT	Sec		0.06		0.06		14
FET100%	Sec		14.99		13.63		-9
FIF50%	L/sec		3.55		3.14		-12
PIF	L/sec		3.92		3.47		-11
FVL ECode			000000		000000		



Lung Volumes				
TLC	Liters	6.35	5.78	91
VC	Liters	4.04	3.57	88
FRC PL	Liters	3.39	4.11	121
ERV	Liters	1.37	1.77	130
RV	Liters	2.29	2.21	97
RV/TLC	%	37	38	

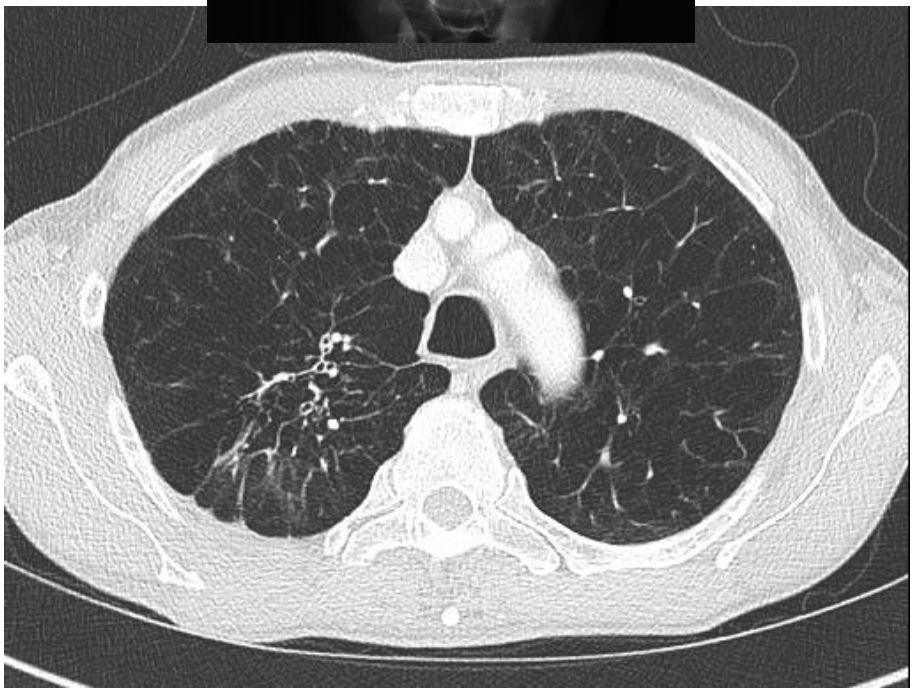


Diffusing Capacity (Hb 16.2)				
DLCO	mL/mmHg/min	22.8	4.0	18
DL Adj	mL/mmHg/min	22.8	3.9	17
DLCO/VA	mL/mHg/min/L	3.95	1.03	26
DL/VA Adj	mL/mHg/min/L		0.99	
VA	Liters		3.91	
IVC	Liters		2.84	



Investigation (2)

- CXR, PNS & Chest CT



Problem list

#1 Severe asthma + COPD emphysema (Ex-smoker)

#2 h/o pulmonary TB (15YA)

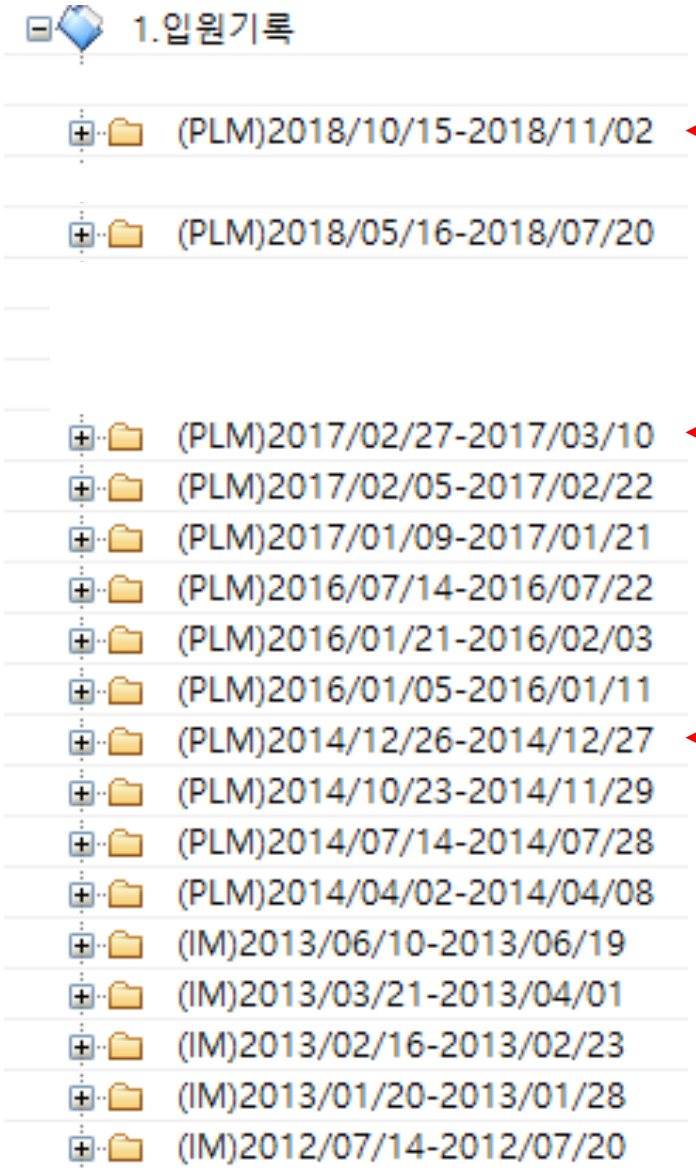
#3 Chronic rhinosinusitis (non-allergic)

#4 Frequent exacerbators (d/t recurrent infection)

TP>

1. ICS/LABA class switch
2. Oral corticosteroid tapering
3. Biologics for severe asthma

Clinical course



Mepolizumab #4
→ Reslizumab #7

사용하고 바로
호흡곤란과
비염증상이 호전

ICS/LABA switch,
oral CS tapering

Omalizumab for 1 year

Diagnosis of severe eosinophilic asthma

TABLE 1 Possible diagnostic scheme for severe eosinophilic asthma (SEA)

Major criteria	Minor criteria
Diagnosis of severe asthma	Late onset of disease
Evidence of high-load eosinophilic disease (persistent blood or sputum eosinophilia detected on ⩾2 occasions)	Upper airway disease (*i.e.* chronic rhinosinusitis, often with nasal polyposis)
Frequent exacerbations (⩾2 per year)	Role of other biomarkers (*e.g.* F_{ENO}, periostin and DPP-4)
Dependence (continuous or intermittent) on oral corticosteroids to achieve asthma control	Fixed airflow obstruction
	Air trapping/presence of mucus plugs

DPP-4: dipeptidyl peptidase-4; F_{ENO}: exhaled nitric oxide fraction.

Roland Buhl et al. Eur Respir J 2017; 49: 1700634

GLOBAL
INITIATIVE
FOR ASTHMA

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A GINA Pocket Guide
For Health Professionals

V2.0 April 2019

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

1 Confirm the diagnosis (asthma/differential diagnoses)

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes

DIAGNOSIS: *"Severe asthma"*

If not done by now, refer to a specialist, if possible.

no

Consider stepping down treatment, OCS first (if used.)

Does asthma become uncontrolled when treatment is stepped down?

yes

Restore previous dose

no

Continue optimizing management

Key

- decision, filters
- intervention, treatment
- diagnosis, confirmation

Assess and treat severe asthma phenotypes

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

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation	
Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

****Consider testing for parasitic infections and treat if present, before type 2 targeted therapy.***

6a Consider ***non-biologic*** treatments

yes

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2 biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

no

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Not currently eligible for biologics

**Off-label*

Assess and treat severe asthma phenotypes *cont'd*

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

Eligible for none?

Return to section **6a**

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

Good asthma response?

yes → Good response to T2-targeted therapy

unclear → Extend trial to 6-12 months

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible

no → Little/no response to T2-targeted therapy

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review **response**

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months
- For **oral treatments:** consider decreasing/stopping OCS first, then stopping other add-on medication
- For **inhaled treatments:** consider decreasing after 3-6 months; continue at least moderate dose ICS
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

yes

If no good response to Type 2-targeted therapy

- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on macrolide*
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchoscopy for alternative/additional diagnoses
  - Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS

no

**Off-label*

8 Continue to **optimize management** as in section **3**, including:

- Inhaler technique
- Adherence
- Comorbidity management
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Notes:

Summary: Management of Severe Asthma

- Stepped pharmacotherapy: ICS/LABA, LAMA, Leukotriene modifier
- Confirm diagnosis of Severe asthma
- Assess adherence/technique, avoid triggers, manage comorbidities
- **Phenotype-specific treatment**
  - Allergic asthma (vs. Non-allergic)
    - ✓ IgE, MAST or Skin prick testing
      → Immunotherapy, Omalizumab
  - Refractory type 2 inflammation while on high-dose ICS
    - ✓ Blood eosinophil ≥150/μL, FeNO ≥20ppb, Sputum eosinophil ≥2%
      → Low dose oral steroid, Biologics for type 2 based on access/cost/preference
  - Type 2 low asthma are not well understood: Th1/Th17 pathway
    - ✓ Obesity (운동/식이/수술/체중감소), smoking (금연), infection
    - ✓ Consider Macrolide or bronchial thermoplasty as add-on therapy
    - ✓ Confirm that high dose ICS or OCS not masking type 2 inflammation
- **Search treatable traits in respiratory diseases**