# Clinical implication of asthma endotypes and phenotypes

Mario Castro MD, MPH

Asthma & Airway Translational Research Unit

University of Kansas Medical Center

Kansas City, Kansas, USA

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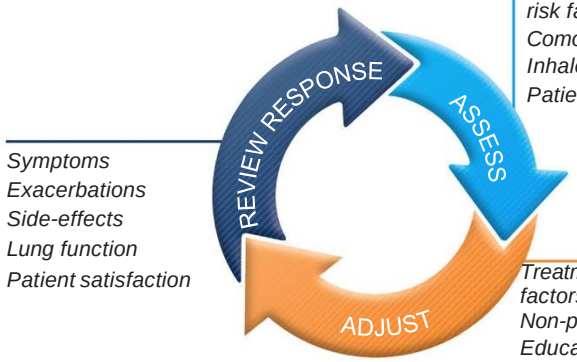
- Speaker: Astra-Zeneca, Genentech, GSK, Regeneron, Sanofi, Teva
- Royalties: Elsevier

# Objectives

- Articulate the differences between phenotype and endotype
- Provide examples of biomarkers which can be used in asthma to predict risk and response to therapy
- Describe the key phenotypes in asthma and potential targets for therapy using the latest GINA guidelines on difficult-to-treat & severe asthma

# Adults & adolescents 12+ years

**Personalized asthma management:**
Assess, Adjust, Review response




*Confirmation of diagnosis if necessary*
*Symptom control & modifiable risk factors (including lung function)*
*Comorbidities*
*Inhaler technique & adherence*
*Patient goals*

*Symptoms*
*Exacerbations*
*Side-effects*
*Lung function*
*Patient satisfaction*

*Treatment of modifiable risk factors & comorbidities*
*Non-pharmacological strategies*
*Education & skills training*
*Asthma medications*

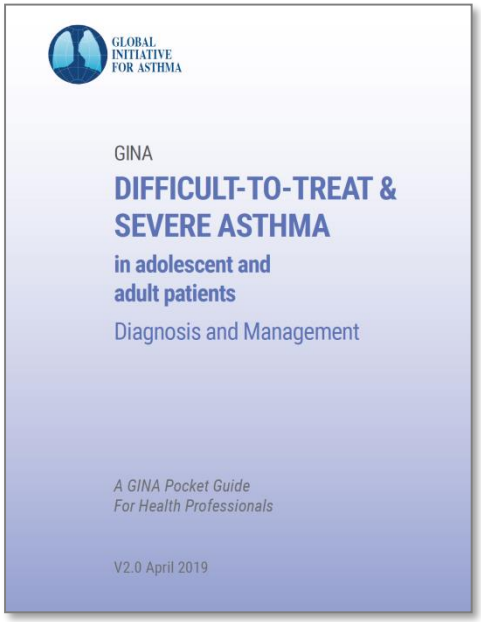
**Asthma medication options:**
Adjust treatment up and down for individual patient needs

| | STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|---|---|---|---|---|---|
| **PREFERRED CONTROLLER** to prevent exacerbations and control symptoms | As-needed low dose ICS-formoterol * | Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol * | Low dose ICS-LABA | Medium dose ICS-LABA | High dose ICS-LABA<br>Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R |
| *Other controller options* | *Low dose ICS taken whenever SABA is taken †* | *Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †* | *Medium dose ICS, or low dose ICS+LTRA #* | *High dose ICS, add-on tiotropium, or add-on LTRA #* | *Add low dose OCS, but consider side-effects* |
| **PREFERRED RELIEVER** | As-needed low dose ICS-formoterol * | | As-needed low dose ICS-formoterol ‡ | | |
| *Other reliever option* | *As-needed short-acting $\beta_2$ -agonist (SABA)* | | | | |

* 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

# Changes in GINA 2019 – severe asthma

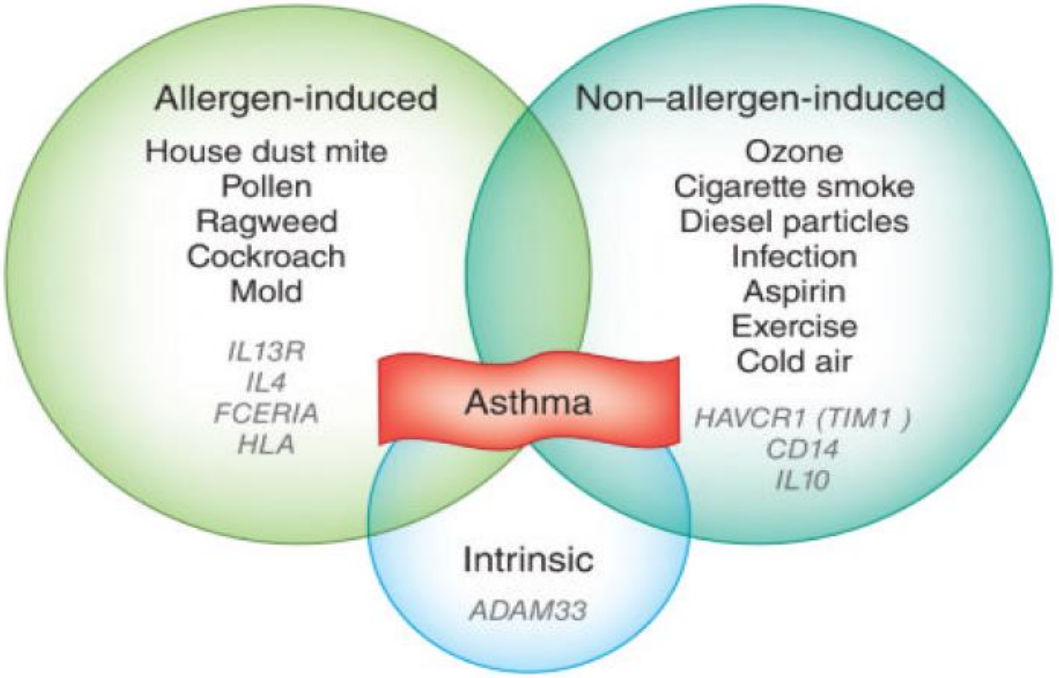
- Pocket guide about difficult-to-treat and severe asthma
  - A practical guide for primary and specialist care
  - Includes a decision tree about assessment and management of adults and adolescents with uncontrolled asthma or exacerbations despite Step 4-5 treatment
  - Includes strategies for clinical settings in which biologic therapy is not available or affordable
  - First published in November 2018
- V2.0 Pocket Guide published April 2018
  - Also included in full GINA 2019 report
  - Includes anti-IL4 receptor alpha (dupilumab)
  - Extension of biologic treatment trial to 6-12 months if response to initial therapy is unclear



# Asthma is a Complex Heterogeneous Disease

- Asthma likely encompasses many different disease variants with different etiologies and pathophysiologies
  - Many phenotypes exist and are determined by clinical characteristics, physiology, triggers, and inflammatory parameters
  - Multiple environmental and genetic factors contribute to the disease

**"Old School"**




Kim et al. *Nat Immunol*. 2010;11:577-584.
Lotvall et al. *J Allergy Clin Immunol*. 2011; 127:355

# Categorizing Asthma by Endotype

- **Phenotype**: The observable characteristics of a disease, such as morphology, development, biochemical or physiological properties, or behaviour.
  - Patients with an identified phenotype of obstructive lung disease may share a cluster of clinical, functional and/or inflammatory features, without any implication of a common underlying mechanism
  - Examples: allergic asthma, aspirin-exacerbated respiratory disease, severe eosinophilic asthma

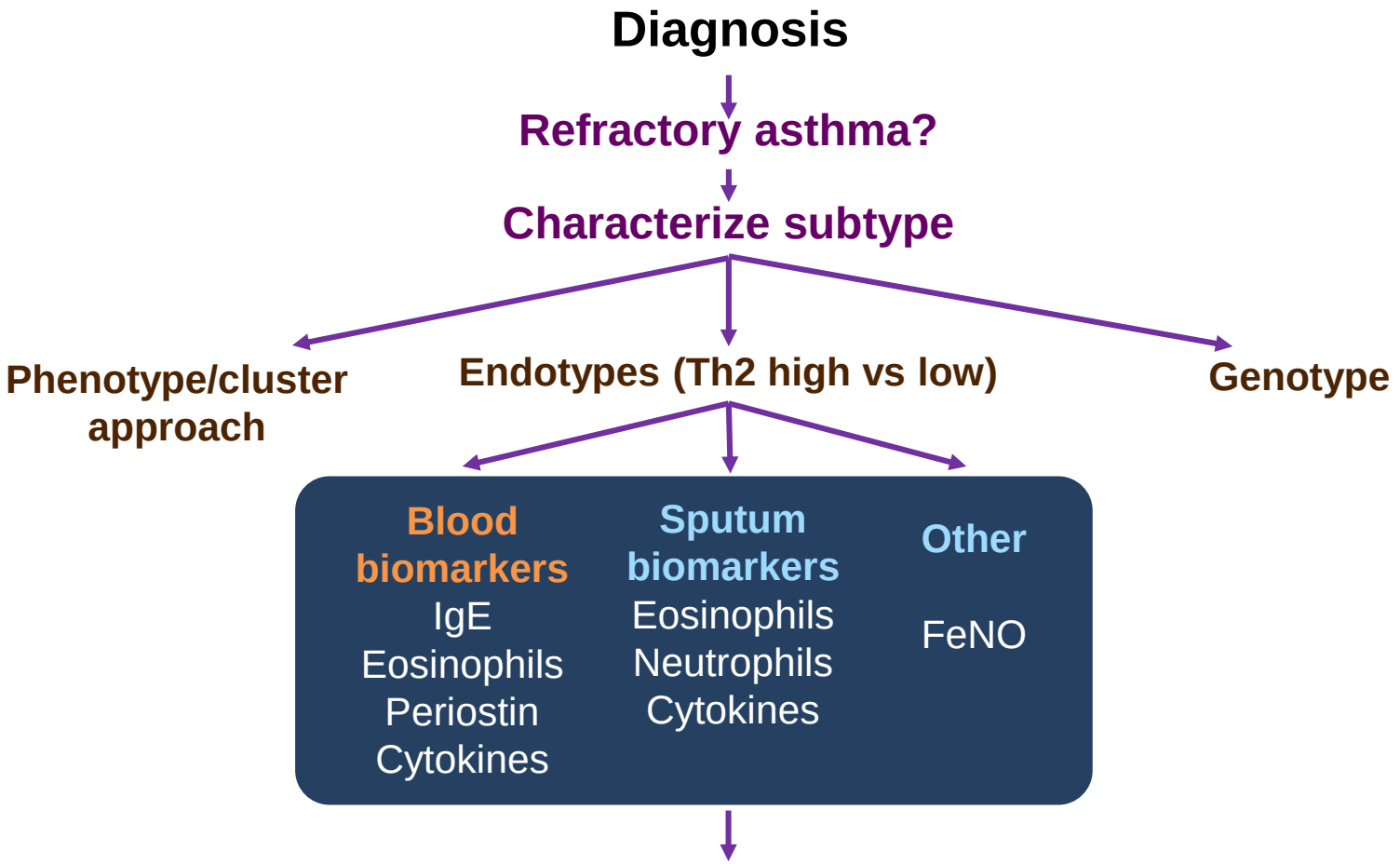
- **Endotype:** A subtype of disease, defined functionally and pathologically by a distinct molecular mechanism or by distinct treatment responses
  - Among patients with obstructive lung disease, there are likely to be several specific endotypes associated with divergent underlying molecular causes, and with distinct treatment responses. These endotypes may or may not align with clinical or inflammatory phenotypes identified from studies limited to asthma or to COPD
  - Examples: emphysema due to alpha1-antitrypsin deficiency

- **Biomarker**: A defined characteristic measured as an indicator of normal biologic processes, pathogenic processes or response to an intervention
  - Potential examples: FeNO, blood eosinophils – but these may not meet quality criteria for biomarkers

Lotvall et al. *J Allergy Clin Immunol*. 2011; 127:355-60.
Anderson, Lancet 2008
Reddel, ERJ Open Research 2019

# Transition to Phenotyping and Endotyping

## Personalized Approach to Asthma




Dunn RM, Wechsler ME. *Clin Pharmacol Ther.* 2015;97:55-65.

# Potential Biomarkers for Asthma Assessment and Management

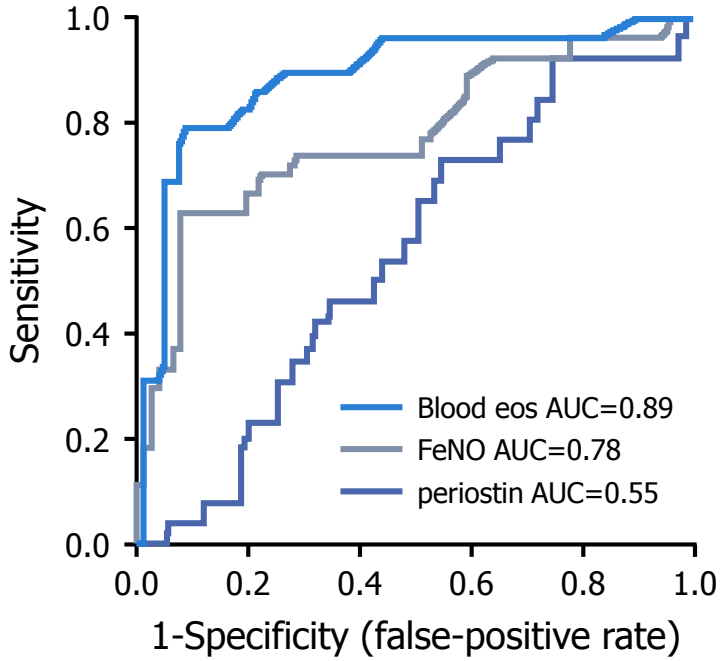
| Biomarker | Characteristics |
|---|---|
| Sputum EOS | • Severe allergic and eosinophilic asthma<br>• Increased exacerbations and poor lung function |
| Blood EOS | • Severe allergic and eosinophilic asthma<br>• Increased exacerbations and poor lung function |
| IgE | • Severe allergic asthma |
| FeNO | • Indicator of oxidative and nitrative stress<br>• Severe allergic and eosinophilic asthma |
| Periostin | • Potentially allergic and eosinophilic asthma |

EOS = eosinophil; FeNO = exhaled nitric oxide fraction; Ig = immunoglobulin.

**1**. Chung KF. *Eur Respir J*. 2014;43:343-373.

# Relation of sputum eosinophils with blood eosinophils, FeNO and periostin

**ROC curve**




**Cut off for each marker to detect sputum eosinophils ≥3%**

| | Threshold | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Blood eosinophils | >0.22 × $10^9$/L | 86 | 79 | 60 | 93 |
| | ≥0.25 × $10^9$/L | 79 | 84 | 64 | 91 |
| | ≥0.27 × $10^9$/L | 78 | 91 | 79 | 91 |
| FeNO | >20ppb | 74 | 57 | 40 | 87 |
| | ≥24ppb | 74 | 63 | 42 | 87 |
| | ≥42ppb | 63 | 92 | 74 | 89 |
| | >50ppb | 56 | 92 | 67 | 84 |
| Serum periostin | >26ng/mL | 54 | 57 | 29 | 77 |

NPV: negative predictive value, PPV: positive predictive value

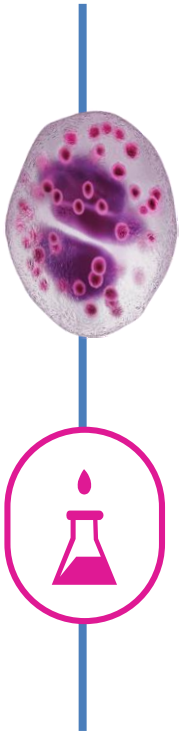
Subjects: 110 patients with mild to moderate asthma
Methods: The relation of sputum eosinophils with blood eosinophils, exhaled nitric oxide level (FeNO), serum periostin was evaluated.

Wagener AH. et al.: Thorax. 70: 115-120, 2015

# Measuring Eosinophils in Clinical Practice

## Peripheral Blood Eosinophils

- Common blood test[1]
- Widely available (complete blood count with differential)[1,2]
- Accuracy varies; levels fluctuate throughout the day[1]
- Increased levels can correlate with exacerbations and loss of control[3]



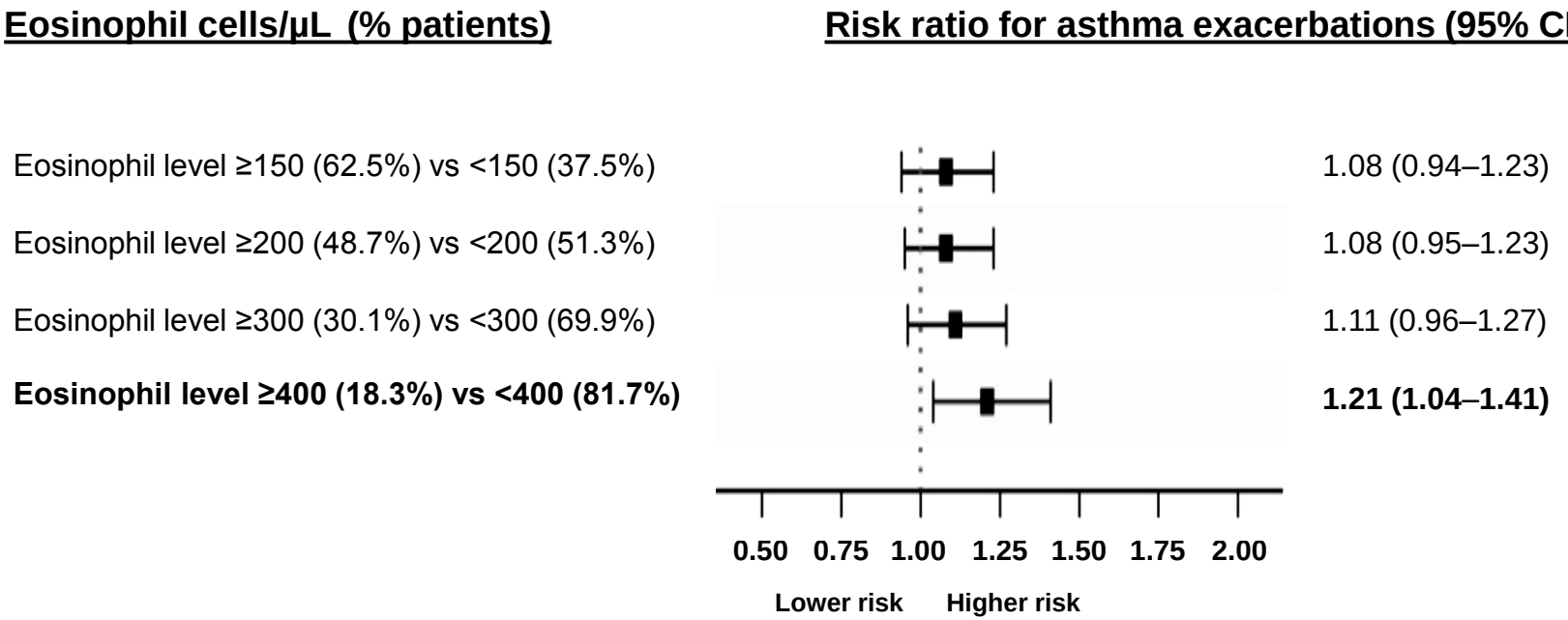
## Sputum Eosinophils

- Accurate predictor of steroid response[1]
- Time consuming[1]
- Labour intensive[1]
- Not readily available[1]

**Peripheral blood eosinophils are a practical biomarker to detect eosinophilic asthma in routine clinical practice and can be used to inform clinical decisions[4,5]**

1. Carr TF, et al. *World Allergy Organ J.* 2016;9:21. 2. George-Gay B and Parker K. *J Perianesth Nurs.* 2003;18:96–114; quiz 115–117. 3. Price DB, et al. *Lancet Respir Med.* 2015;3:849–858. 4. Katz LE, et al. *Ann Am Thorac Soc.* 2014;11:531–536. 5. GINA. Global Strategy for Asthma Management and Prevention. 2017. http://ginasthma.org/gina-reports/. Accessed 13 March 2018.

# Patients with High EOS Levels Were More Likely to Have Inadequately Controlled Asthma




A retrospective cohort study (N=2392) was conducted to assess the association between high EOS levels and the risk of future exacerbations in the following 12 months

- Exacerbations were defined as asthma outpatient visits that required systemic CS, ED visits, or hospitalizations

Patients with EOS levels ≥400 cells/μL were significantly more likely to have inadequately controlled asthma and increased exacerbations

- 30% increase in asthma exacerbation rate (rate ratio 1.31; 95% CI, 1.07-1.60; *P*=0.009)

CI = confidence interval; CS = corticosteroid; ED = emergency department.

**1.** Zeiger RS, et al. *J Allergy Clin Immunol.* 2014;2(6):741-750.

# Elevated Peripheral Blood Eosinophil Levels Correlate with Several Asthma Outcomes

**Unadjusted rate ratio or risk ratio of asthma outcomes over a 12-month period, by blood eosinophil count ≥400/mm$^3$ versus <400/mm$^3$ as determined during the previous year[a]**

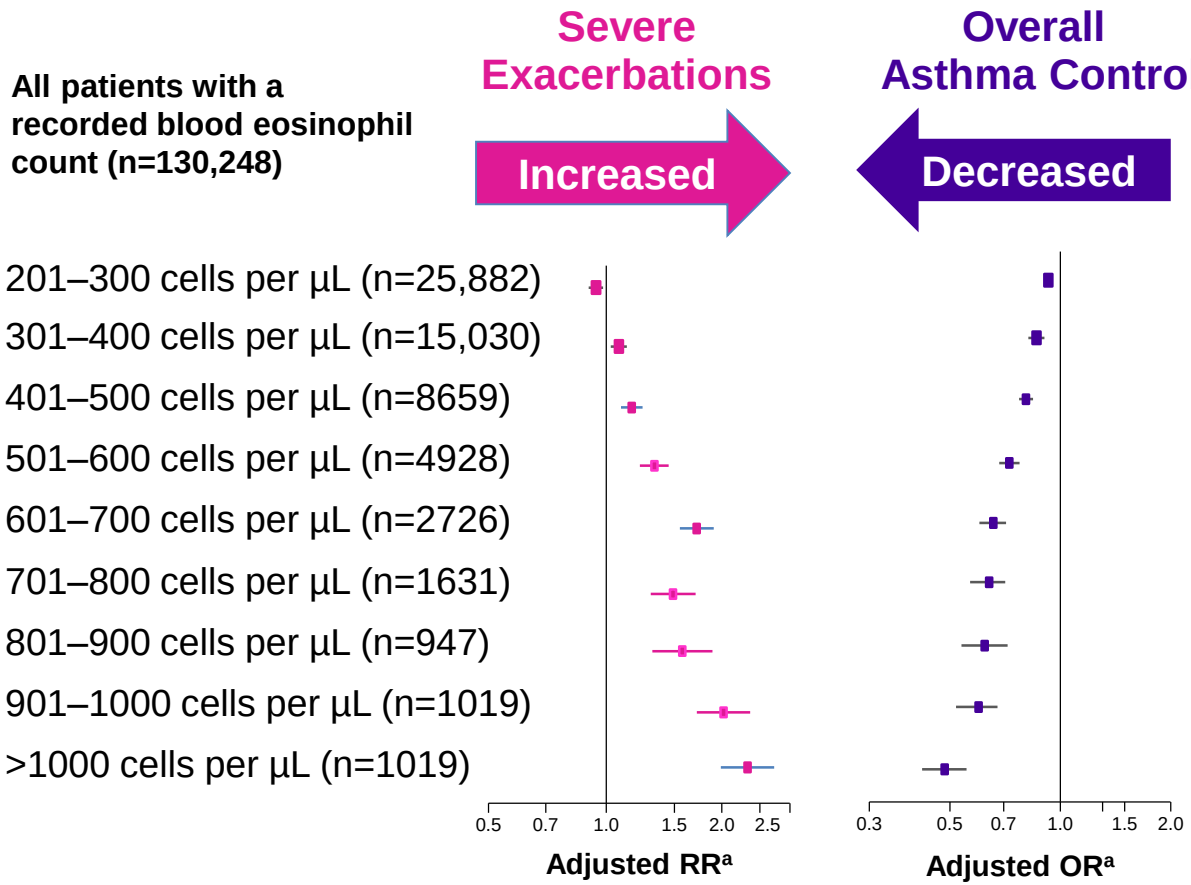
| Asthma Outcomes Over 12 months | Eosinophil ≥400/mm$^3$, No. (%) (n=437) | Eosinophil <400/mm$^3$, No. (%) (n=1955) | Unadjusted Rate Ratio or Risk Ratio (95% CI)[a] | *P* value[b] |
|---|---|---|---|---|
| Asthma exacerbation | 0.57[c] | 0.37[c] | 1.52 (1.23–1.88) | <0.001 |
| Any asthma exacerbation | 142 (32.5) | 465 (23.8) | 1.37 (1.17–1.60) | <0.001 |
| ≥2 Asthma exacerbations | 50 (11.4) | 154 (7.9) | 1.45 (1.07–1.96) | 0.02 |
| Any asthma ED visit | 46 (10.5) | 116 (5.9) | 1.77 (1.28–2.46) | <0.001 |
| Any asthma hospitalisation | 19 (4.3) | 38 (1.9) | 2.24 (1.30–3.84) | 0.004 |
| Any asthma ED and/or hospitalisation | 46 (10.5) | 120 (6.1) | 1.71 (1.24–2.37) | 0.001 |
| ≥7 SABA canisters dispensed | 150 (34.3) | 475 (24.3) | 1.41 (1.21–1.64) | <0.001 |

[a] Outcomes occurring in the year 2011 according to electronic pharmacy and healthcare data, by blood eosinophil count determined in the year 2010.
[b] Negative binomial and Poisson regression models with robust error variance were used to estimate the rate ratio and risk ratio, respectively, their 95% CIs, and to derive the *P* values.
[c] Data are rate/y. ED=emergency department; SABA=short-acting $\beta_2$-agonist.

Zeiger RS, et al. *J Allergy Clin Immunol Pract*. 2014;2:741–750.

# Elevated Peripheral Blood Eosinophils are Associated with Worse Asthma Control and Increased Risk of Severe Exacerbations

**All patients with a recorded blood eosinophil count (n=130,248)**




*Linear relationship between increasing blood eosinophil count and subsequent exacerbations over one year*

[a]Data from medical records of asthmatics,12–80 years of age, with 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients assigned to 9 eosinophil count categories compared with a reference category of 200 cells per µL or less (N=68,407). Adjusted for age, sex, body-mass index, smoking status and Charlson comorbidity index score.

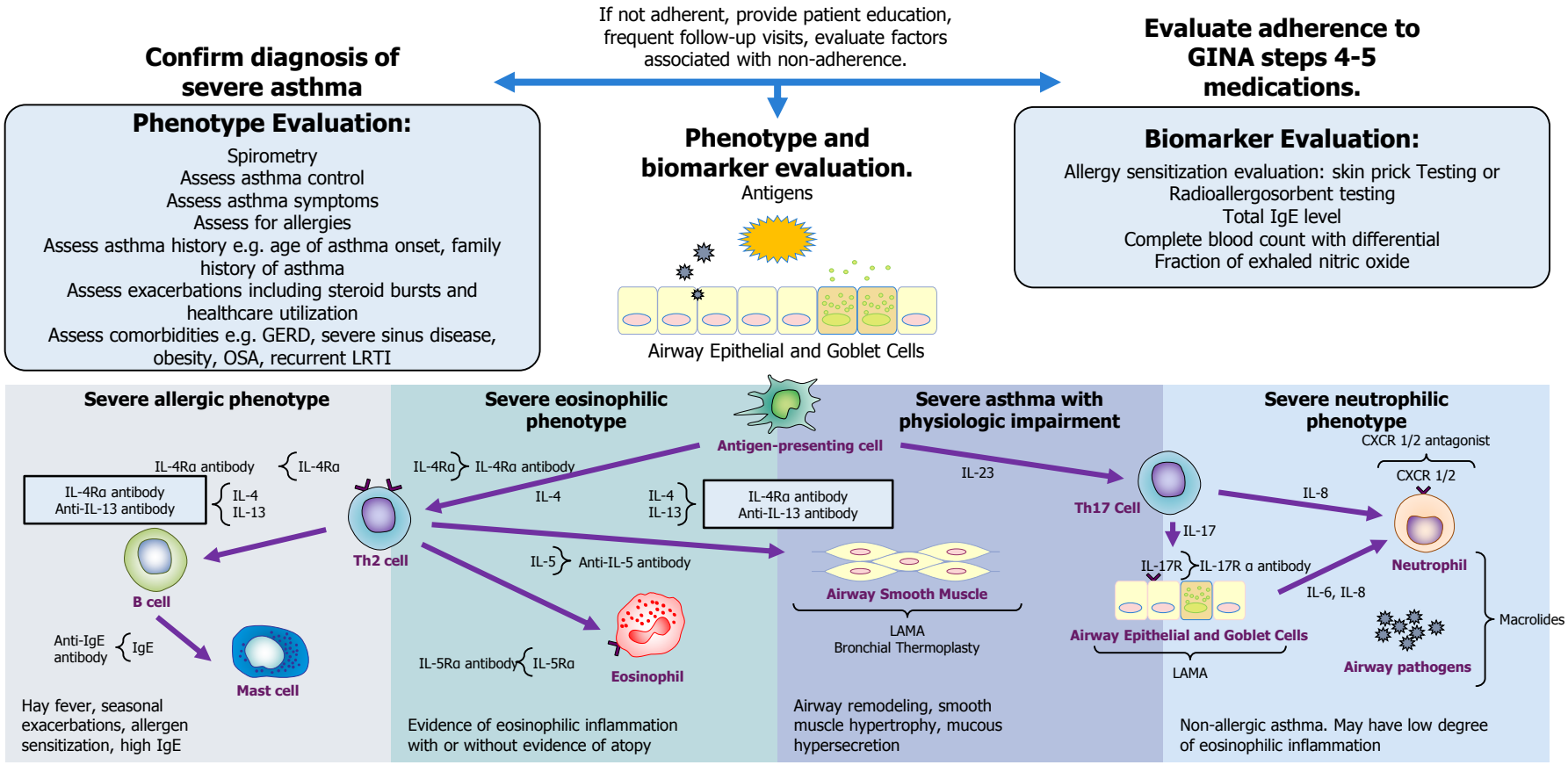
[b]Sub-population of patients with available blood eosinophil counts to two decimal places.

# Potential phenotype-targeted therapies in severe asthma

| Characteristic | Associations | Specifically-targeted treatments |
|---|---|---|
| **Severe allergic asthma** | High eosinophil<br>High serum IgE<br>High FeNO | Anti-IgE (adults and children)<br>Anti-IL-4/IL-13<br>IL-4/R |
| **Eosinophilic asthma** | High serum IgE<br>Recurrent exacerbations<br>High FeNO | Anti-IL-5<br>Anti-IL-4/-13<br>IL-4/R |
| **Non-eosinophilic, neutrophilic asthma** | Corticosteroid insensitivity<br>Bacterial infections | Anti-IL-8<br>CXCR2 antagonists<br>Anti-LTB4 (adults and children)<br>Macrolides (adults and children) |
| **Chronic airflow obstruction** | Airway wall remodelling as increased airway wall thickness | Anti-IL-13<br>Bronchial thermoplasty |
| **Recurrent exacerbations** | Eosinophils in sputum<br>Reduced response to ICS ± OCS | Anti-IL-5<br>Anti-IgE (adults and children) |
| **Corticosteroid insensitivity** | High neutrophils in sputum | p38 MAPK inhibitors<br>Theophylline (adults and children)<br>Macrolides (adults and children) |

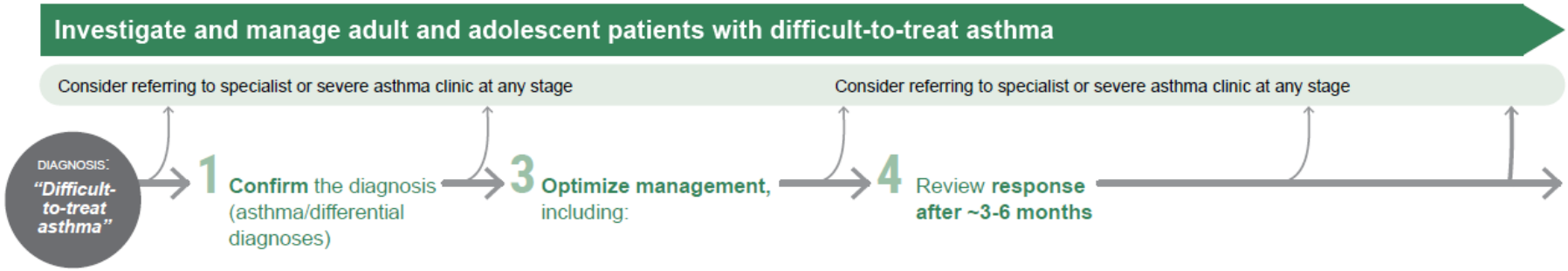
International ERS/ATS Guidelines Eur Respir J 2014;43:343–73

# Add-on therapy by phenotype in severe asthma




Opina MT. et al.: Curr Allergy Asthma Rep. 17: 10, 2017

GP OR SPECIALIST CARE



SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

**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

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

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## 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

SPECIALIST AND PRIMARY CARE IN COLLABORATION

## Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review **response** → 8 Continue to **optimize management**

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

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

**1** **Confirm** the diagnosis (asthma/differential diagnoses)

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

**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

*Key*

decision, filters

intervention, treatment

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- Overuse of SABA relievers
- Medication side effects
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**3** **Optimize management,** including:

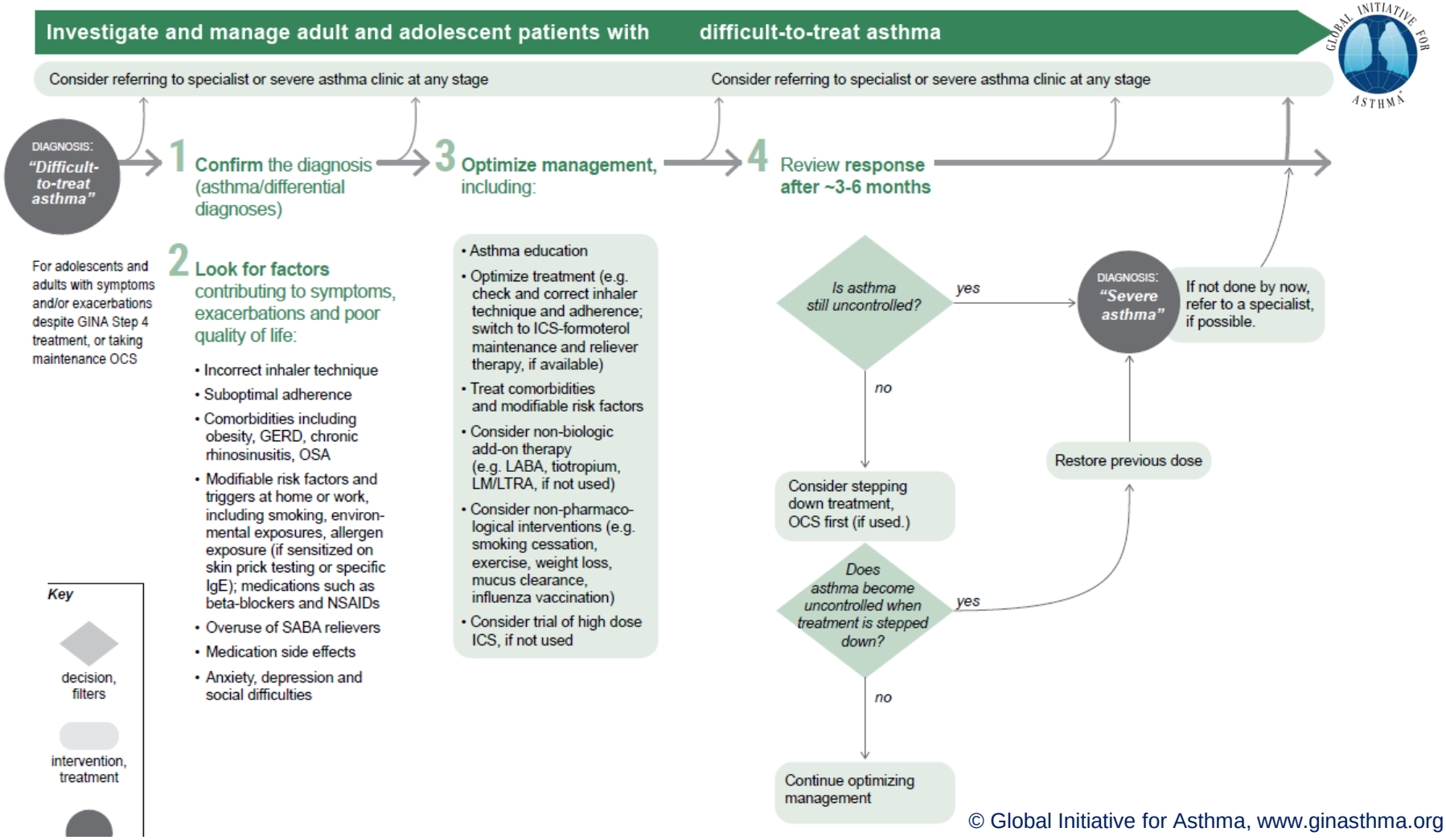
- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)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

*Key*

decision, filters

intervention, treatment

GP OR SPECIALIST CARE



SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## 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

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

- ***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<br>• FeNO ≥20 ppb and/or<br>• Sputum eosinophils ≥2%, and/or<br>• Asthma is clinically allergen-driven and/or<br>• Need for maintenance OCS<br>(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)***

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## Assess and treat severe asthma phenotypes

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

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### Type 2 inflammation

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| *Note: these are not the criteria for add-on biologic therapy (see* **6b***)* | |

*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)

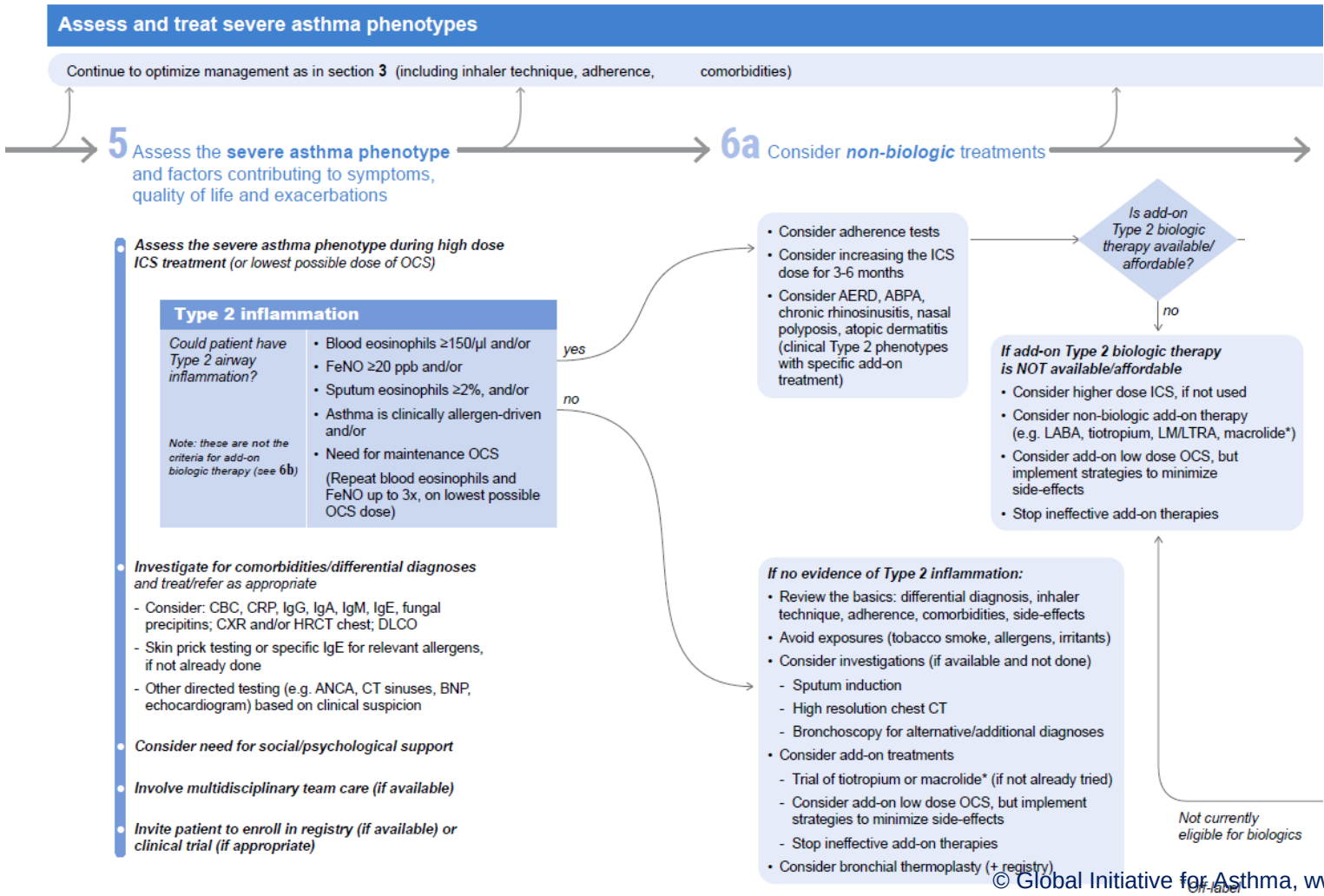
*no*

- ***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)***

***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)

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE



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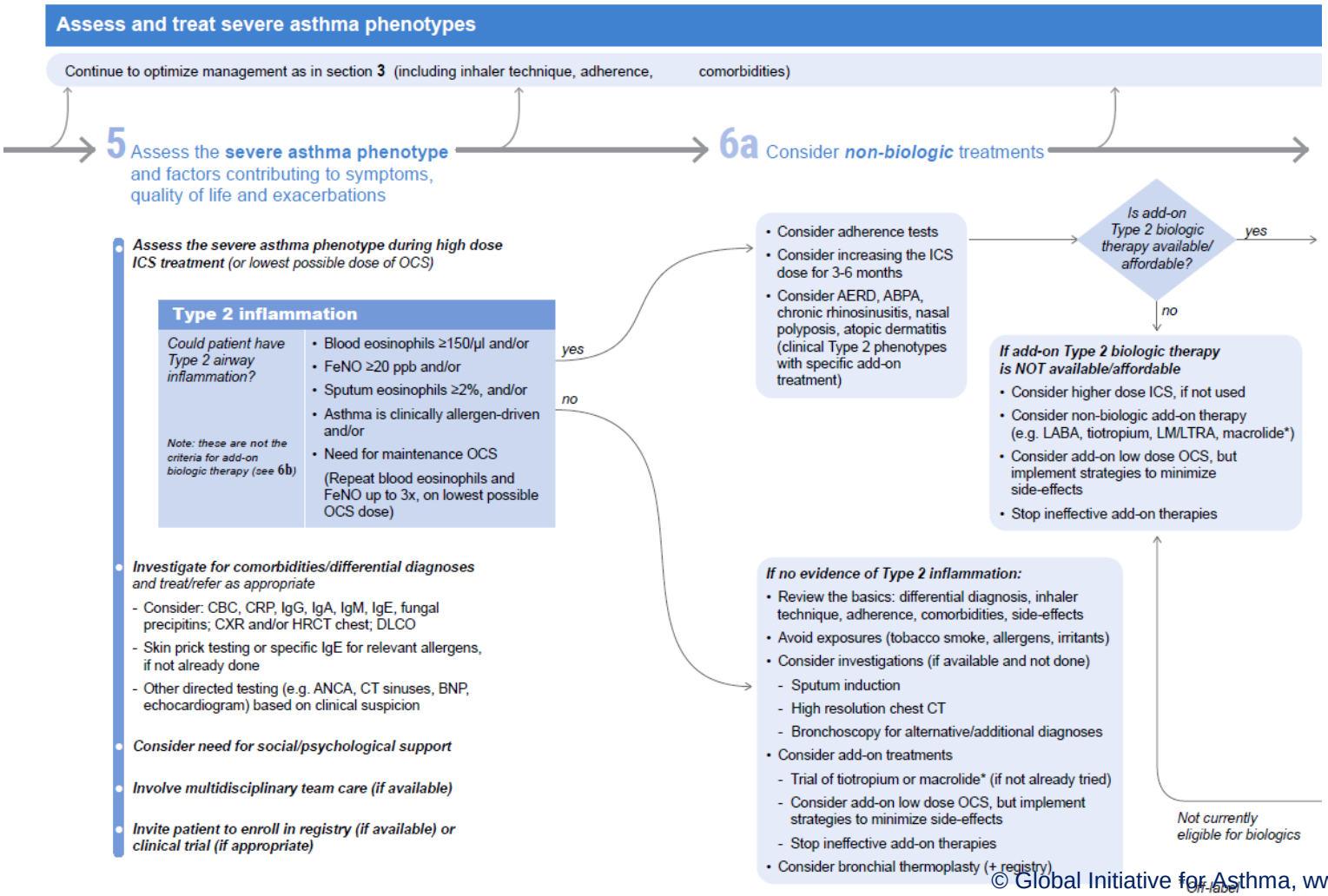

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## 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

*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

*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?*

*Eligible for none?*
*Return to section* **6a**

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

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## Assess and treat severe asthma phenotypes *cont'd*

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

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**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*

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

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

## 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

*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

*no* / *no*

**Anti-IL4R**

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

*… for severe eosinophilic asthma?*

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

*… or because of need for maintenance OCS?*

*Eligible for none?*
*Return to section* **6a**

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

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

*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 ++

*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

*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

SPECIALIST AND PRIMARY CARE IN COLLABORATION

## 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

yes

***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

SPECIALIST AND PRIMARY CARE IN COLLABORATION

## 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

yes →

***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

no →

***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

**Off-label*

SPECIALIST AND PRIMARY CARE IN COLLABORATION

## 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

yes →

***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

no →

***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
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  - 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

**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:**

# Phenotypes of severe asthma

## *- Personalized medicine with biologics*

- Assess phenotypes utilizing lowest levels of blood/sputum eosinophils, FeNO associated with good response to biologics
- Current biologic therapy for the severe uncontrolled asthma phenotype is highly effective but likely represents less than 60% of patients
- Local regulatory/payer criteria may impact selection
- Targeted phenotype therapy can lead to personalized medical therapy for asthma