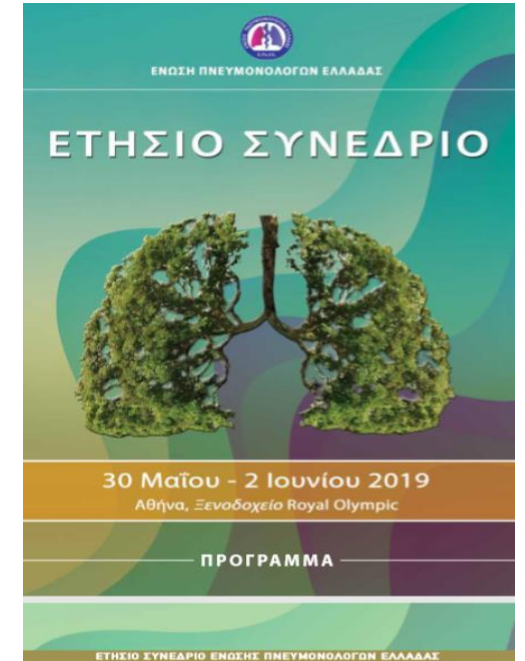


# Επιλέγοντας τους ασθενείς με σοβαρό άσθμα



Αθηνά Γόγαλη MD, PhD

Επιμελήτρια Α΄, Πανεπιστημιακή Πνευμονολογική Κλινική Ιωαννίνων

e-mail: [athenagogali@yahoo.com](mailto:athenagogali@yahoo.com)



# Definitions: uncontrolled, difficult-to-treat and severe asthma

---

- **Uncontrolled asthma** includes one or both of the following:
  - Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
  - Frequent exacerbations ( $\geq 2$ /year) requiring oral corticosteroids (OCS), or serious exacerbations ( $\geq 1$ /year) requiring hospitalization.
- **Difficult-to-treat asthma** is asthma that is:
  - uncontrolled despite GINA Step 4 or 5 treatment (e.g. medium or high dose inhaled corticosteroids (ICS) with a second controller; maintenance OCS),  
OR
  - that requires such treatment to maintain good symptom control and reduce the risk of exacerbations.

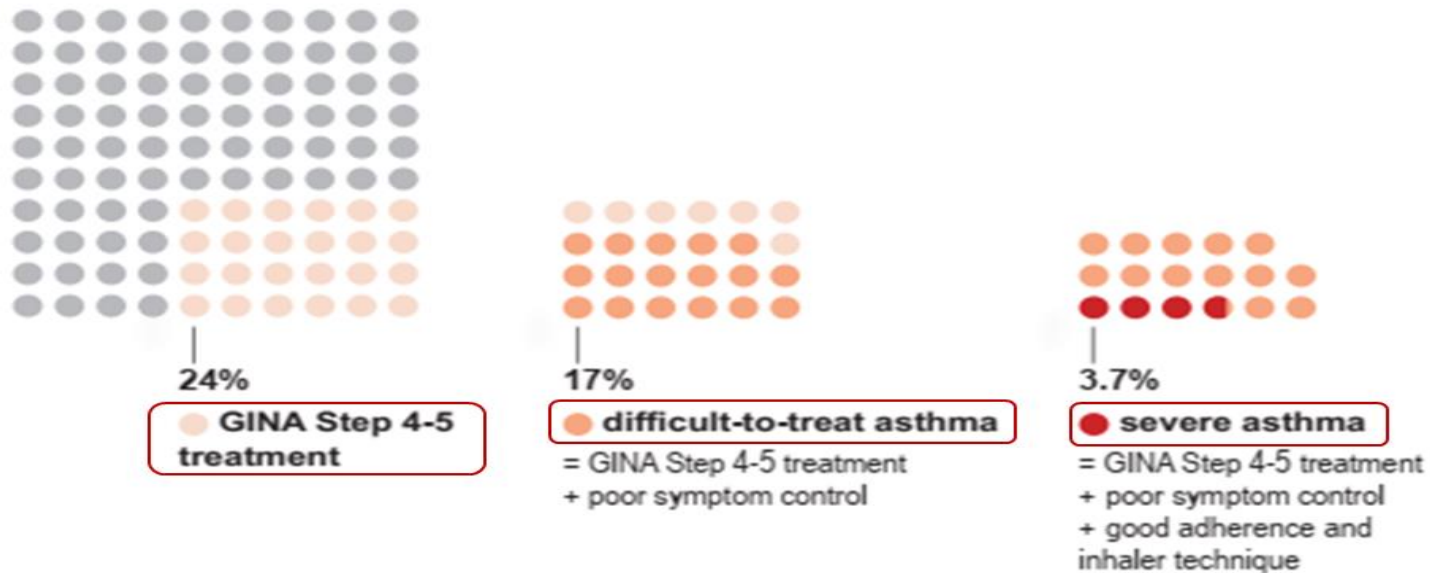
*In many cases, asthma may appear to be difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.*

# Definitions: uncontrolled, difficult-to-treat and severe asthma

- **Severe asthma** is a subset of difficult-to-treat asthma. It means asthma:
  - that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors  
or
  - that worsens when high dose treatment is decreased

**Prevalence:** how many people have severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



These data are from a Dutch population survey of people ≥18 years with asthma<sup>2</sup>

# Assessing asthma severity

---

- **How?**

- Asthma severity is assessed **retrospectively** from the level of treatment required to control symptoms and exacerbations

- **When?**

- Assess asthma severity after patient has been on controller treatment for several months
- Severity is not static – it may change over months or years, or as different treatments become available

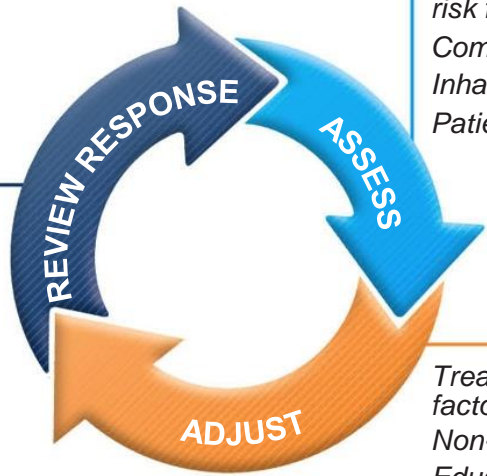
- **Categories of asthma severity**

- *Mild asthma*: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
- *Moderate asthma*: well-controlled with Step 3 (low-dose ICS/LABA)
- *Severe asthma*: requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

# Adults & adolescents 12+ years

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

Symptoms  
Exacerbations  
Side-effects  
Lung function  
Patient satisfaction



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

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

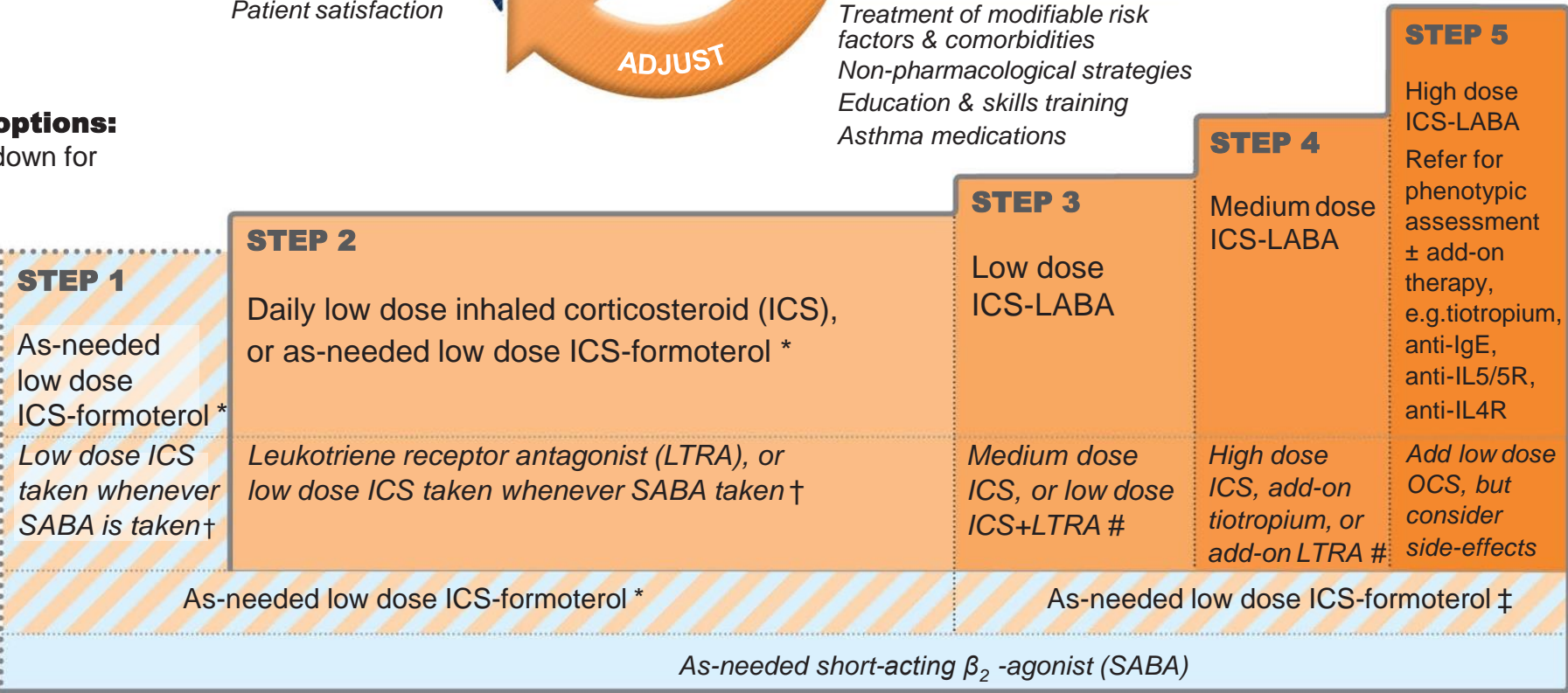
**Asthma medication options:**  
Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**  
to prevent exacerbations and control symptoms

Other controller options

**PREFERRED RELIEVER**

Other reliever option



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

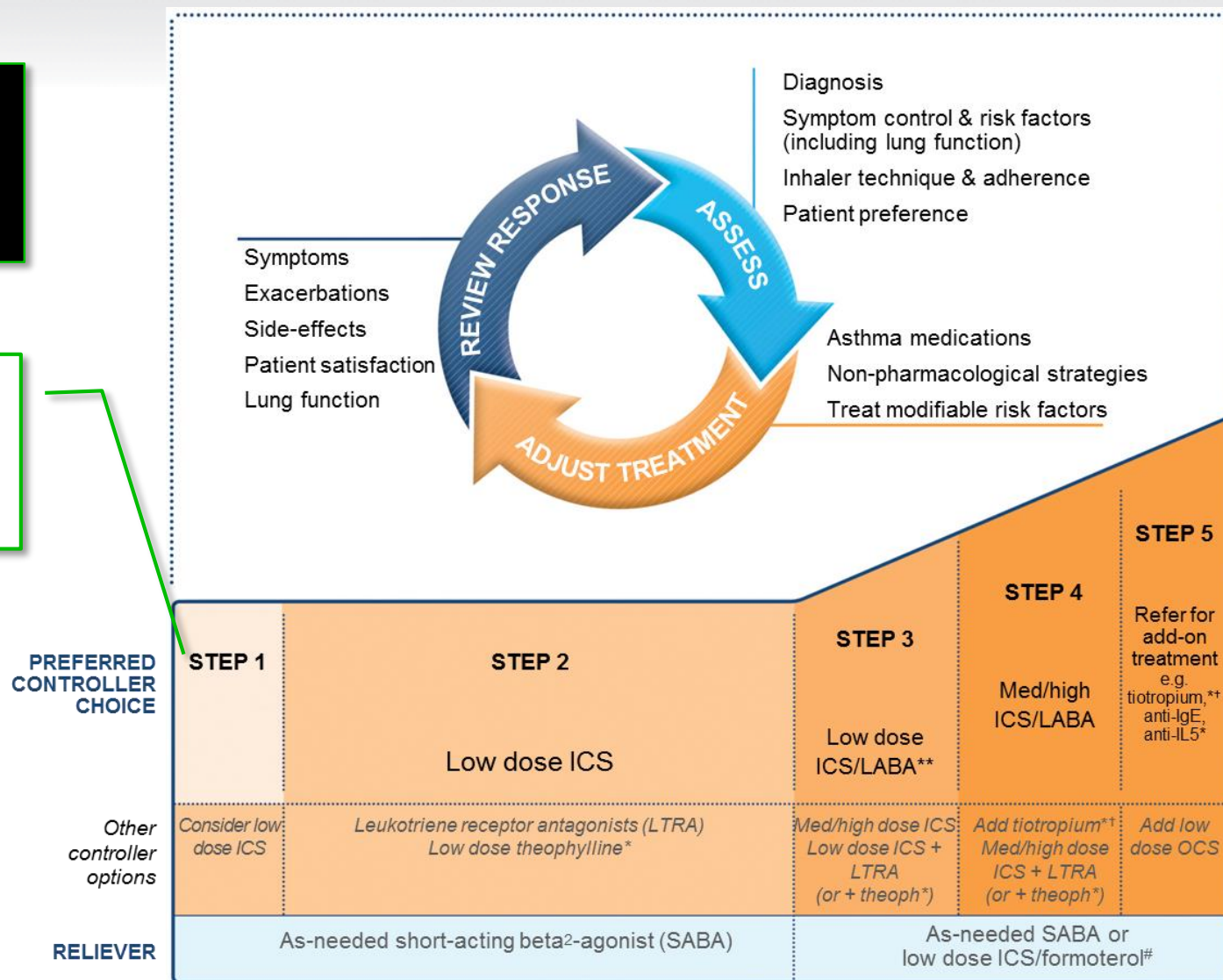
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy  
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV<sub>1</sub> >70% predicted



# GINA 2018 – main treatment figure

Step 1 treatment is for patients with symptoms <twice/month and no risk factors for exacerbations

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'



\*Not for children <12 years

\*\*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

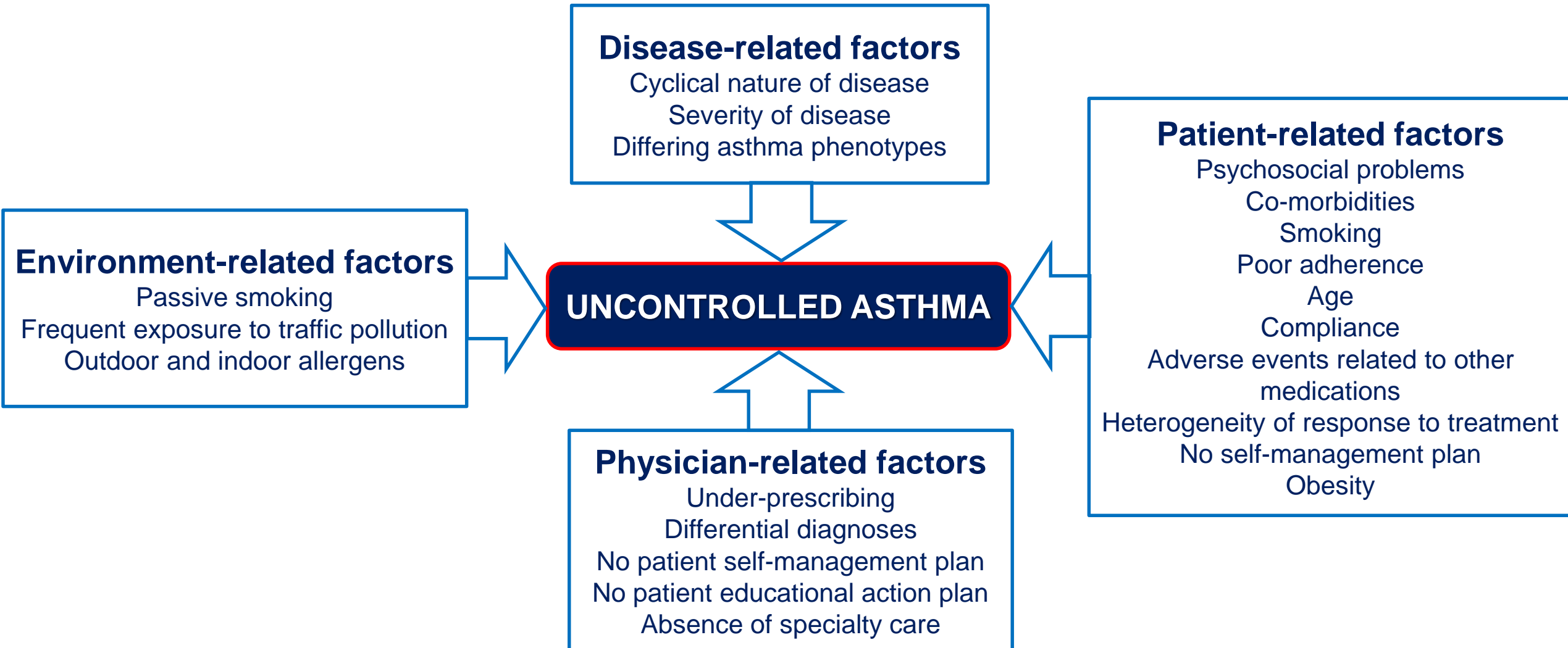
# High-dose ICS ?

TABLE 1 High-dose inhaled corticosteroids proposed by the European Respiratory Society (ERS)/American Thoracic Society (ATS) [2] and the Global Initiative for Asthma (GINA) [18]

	ERS/ATS high dose µg	GINA high dose µg
<b>Beclomethasone dipropionate (chlorofluorocarbon)</b>	≥2000	>1000
<b>Beclomethasone dipropionate (hydrofluoroalkane)</b>	≥1000	>400
<b>Budesonide</b>	≥1600	>800
<b>Ciclesonide</b>	≥320	>320
<b>Fluticasone furoate</b>	NA	200
<b>Fluticasone propionate</b>	≥1000	>500
<b>Mometasone furoate</b>	≥800	≥440
<b>Triamcinolone acetonide</b>	≥1200	>2000

NA: not applicable.

# Uncontrolled asthma: a multifactorial issue





# Assessing patients with suspected severe asthma

---

- **Step 1: Is it really asthma?**



- **Step 2 : Adherence to treatment/ inhaler technique**



- **Step 3: Assessing comorbidities and contributing factors**



- **Step 4 : Severe asthma phenotyping**

# Step 1: Is it really asthma?

---

## Diseases that can masquerade as severe asthma

### Adults

- Vocal cord dysfunction
- Hyperventilation with panic attacks
- COPD
- Congestive heart failure
- Adverse drug reaction (e.g. ACE inhibitors)
- Bronchiectasis/cystic fibrosis
- Hypersensitivity pneumonitis
- **Hypereosinophilic syndromes**
- **Allergic bronchopulmonary aspergillosis**
- **Churg–Strauss syndrome**
- Bronchiolitis obliterans
- Pulmonary embolus
- Endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture)
- Acquired tracheobronchomalacia
- Herpetic tracheobronchitis

### Children

- Vocal cord dysfunction
- Bronchiolitis
- Recurrent aspiration/reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression
- Foreign body
- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumor
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease

***Modified from Chung KF, et al. Eur Respir J 2014 (ERS/ATS Guidelines).***

# Systematic Assessment of Difficult to Treat Asthma - RBH/NHLI UK

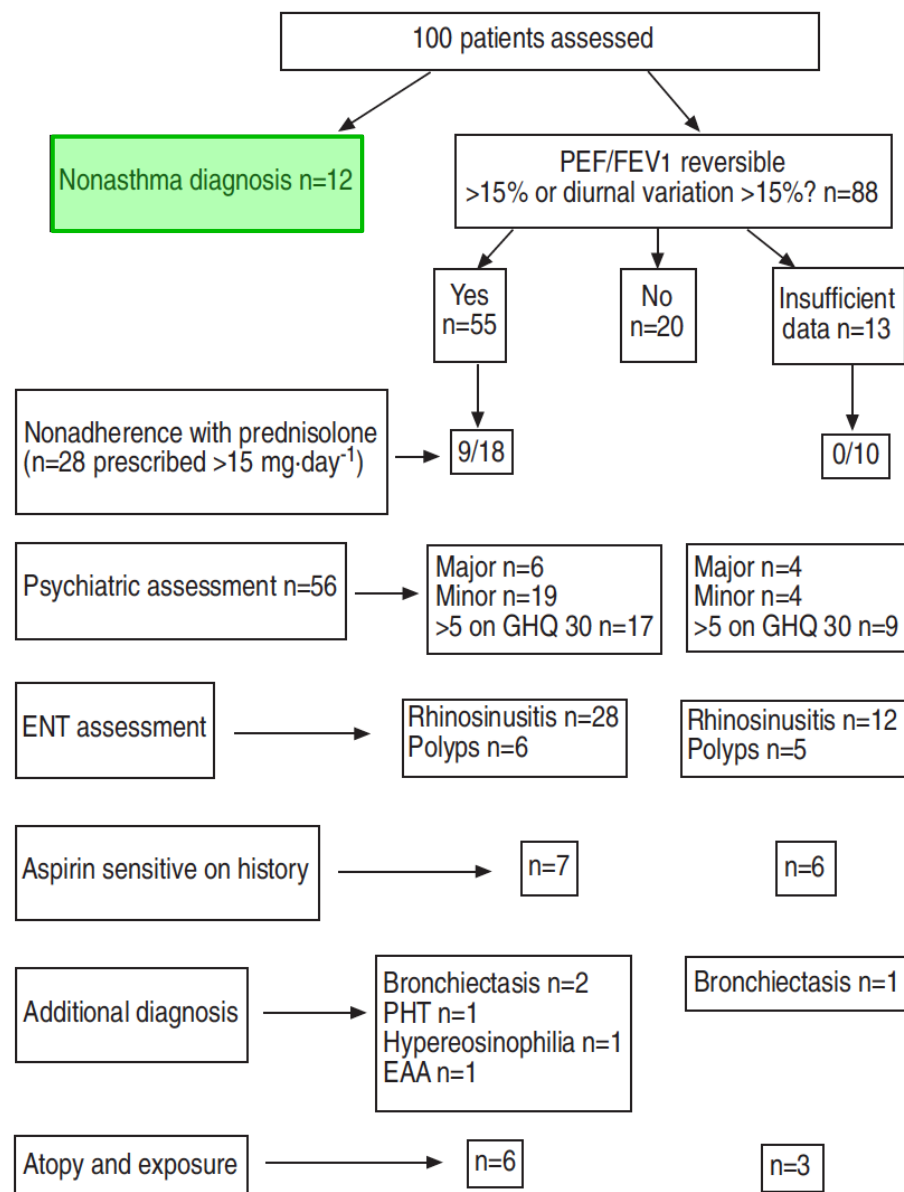
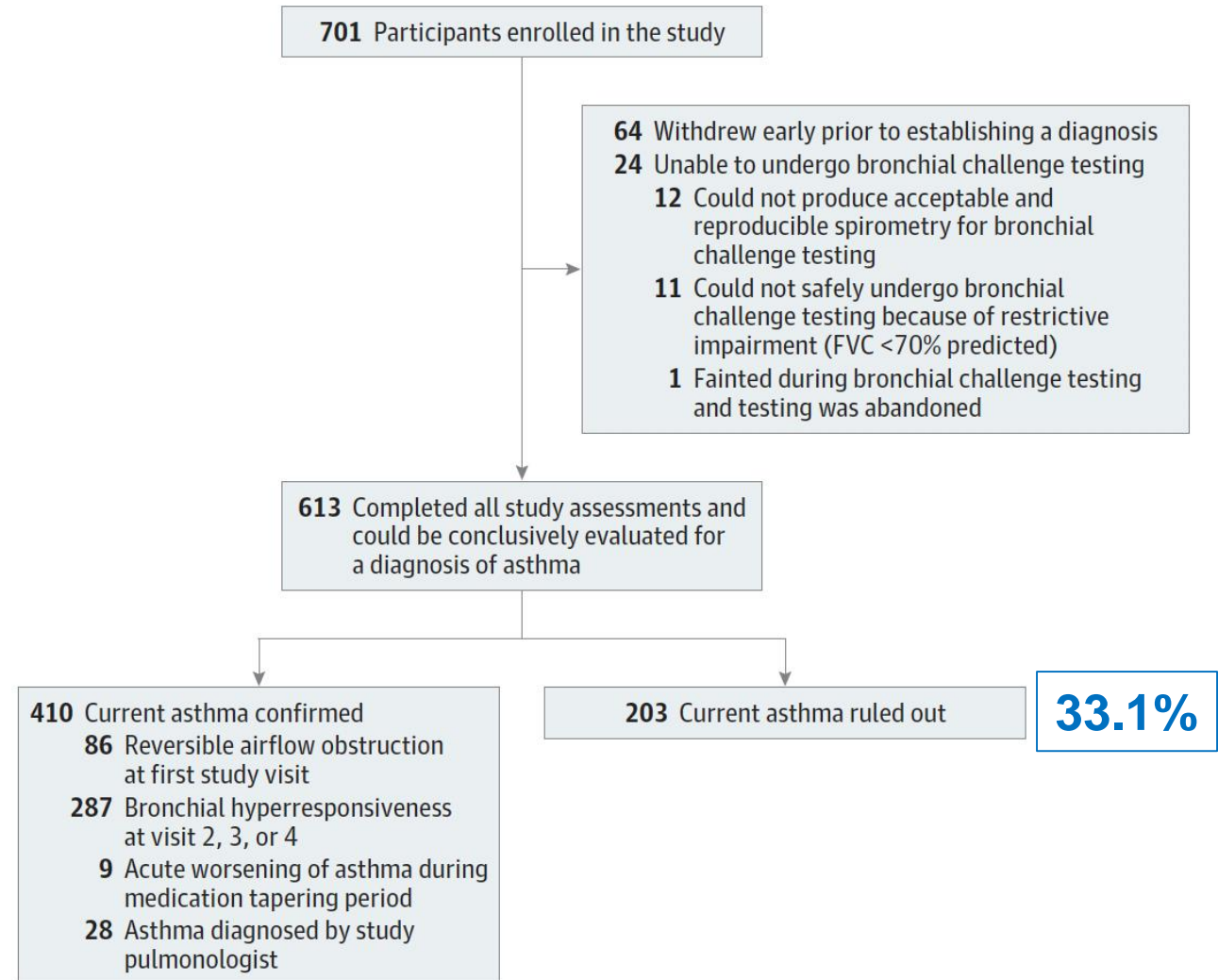
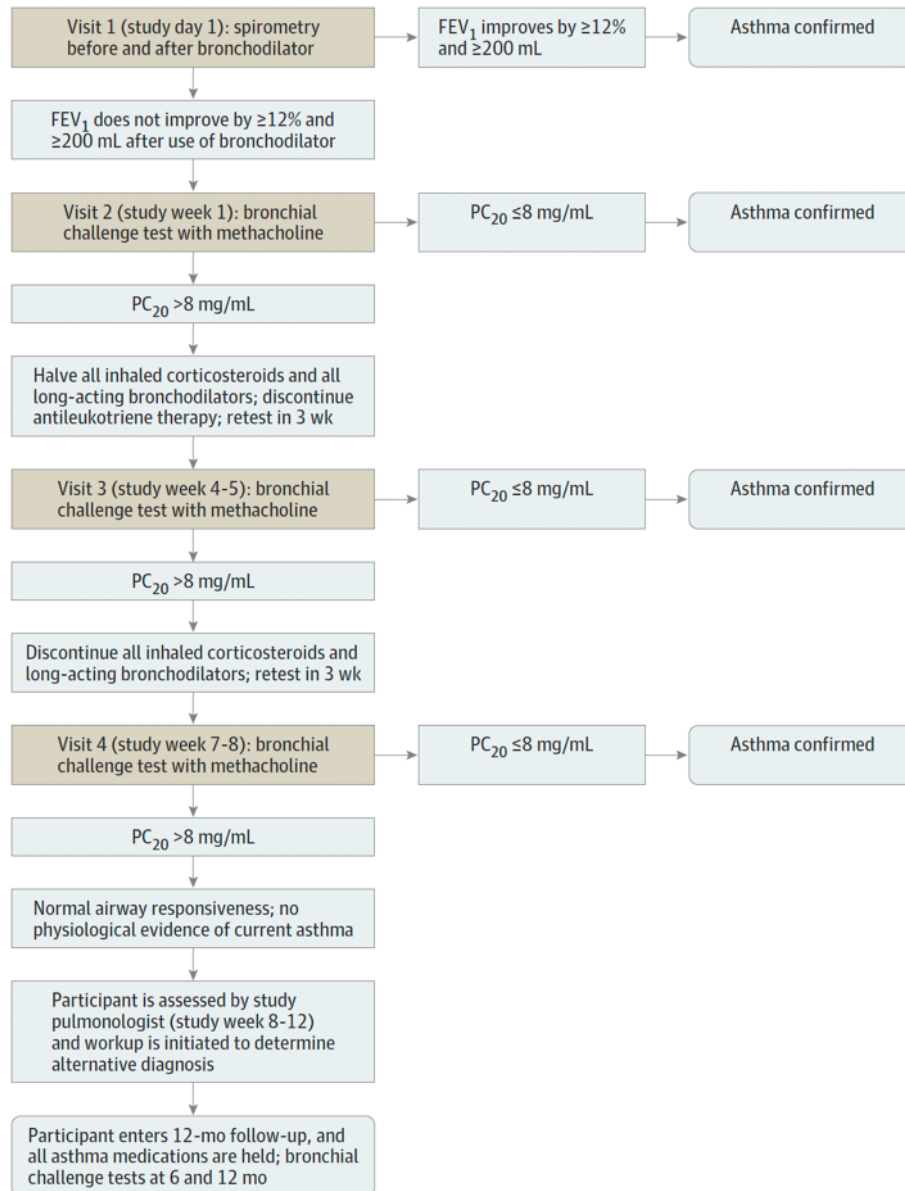


Table 1. – Diagnoses in patients without asthma

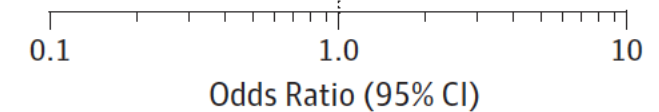
Chronic obstructive pulmonary disease	6
Emphysema ( $\alpha_1$ -antitrypsin deficient)	1
Cystic fibrosis	1
Cardiomyopathy	1
Obliterative bronchiolitis	1
Respiratory muscle incoordination	1
Severe anxiety and vocal cord dysfunction	1

# Reevaluation of diagnosis in adults with physician-diagnosed asthma



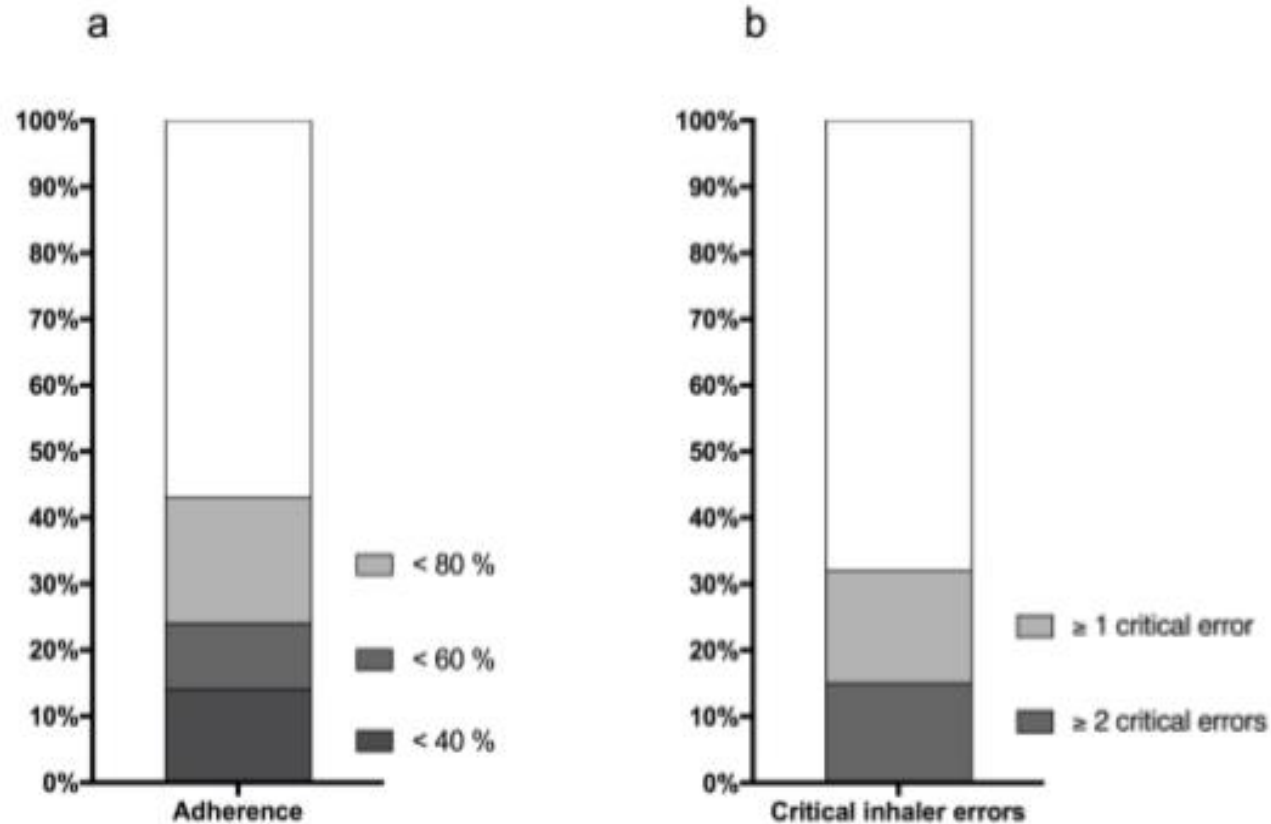
# Reevaluation of diagnosis in adults with physician-diagnosed asthma

	Patients With Asthma Confirmed, No./Total No. (%)	Patients With Asthma Ruled Out, No./Total No. (%)	Absolute Risk Difference (95% CI)	Odds Ratio (95% CI)	Decreased Risk of Current Asthma	Increased Risk of Current Asthma	P Value
Age at diagnosis (per year)			-0.19 (-0.60 to 0.22)	0.99 (0.96 to 1.02)			.41
Diagnosis by a specialist	142/317 (44.8)	52/144 (36.1)	5.95 (-2.84 to 14.74)	1.37 (0.85 to 2.21)			.20
Airflow testing done in community at diagnosis	177/317 (55.8)	63/144 (43.8)	10.93 (2.39 to 19.48)	1.79 (1.13 to 2.85)			.01
Daily use of asthma medications	163/317 (51.4)	59/144 (41.0)	8.70 (0.45 to 16.94)	1.63 (1.04 to 2.55)			.03
FEV <sub>1</sub> % predicted (per increase of 1%)			-0.80 (-1.02 to -0.58)	0.95 (0.94 to 0.97)			<.001
Dyspnea within 12 mo of study entry	269/317 (84.9)	111/144 (77.1)	-2.56 (-14.93 to 9.82)	0.87 (0.47 to 1.60)			.64
Wheeze within 12 mo of study entry	261/317 (82.3)	92/144 (63.9)	19.11 (8.17 to 30.05)	2.57 (1.50 to 4.39)			.001
AQLQ mean total score (per 1-point increase)			-1.38 (-5.56 to 2.80)	0.90 (0.71 to 1.15)			.40



## Step 2 : Adherence to treatment/ inhaler technique

**Figure 3:** Proportions of patients with difficult-to-control asthma with adherence for inhaled corticosteroids < 80 %, < 60 % and < 40 %, respectively (a) or at least one or two critical inhaler errors (b).





## Step 3: Assessing comorbidities and contributing factors

---

- Persistent allergic rhinitis 23.1 %
- Rhinosinuitis 31.3 %
- OSA (high risk) 44.3 %
- GERD 34.2 %
- Anxiety/depression symptoms 24.3 %
- Dysfunctional breathing 29.9 %
- Obesity 30.8 %
- Bronchiectasis 31.5 %
- Exposures
  - Allergen exposure 13.7 %
  - Use of NSAID, salicylates, beta-blockers 23.1 %
  - Current smoking 6.0 %

## Recognition and management of severe asthma: A Canadian Thoracic Society position statement

J. Mark FitzGerald<sup>a</sup>, Catherine Lemiere<sup>b</sup>, M. Diane Lougheed<sup>c</sup>, Francine M. Ducharme<sup>d</sup>, Sharon D. Dell<sup>e</sup>, Clare Ramsey<sup>f</sup>, M. Connie L. Yang<sup>g</sup>, Andréanne Côté<sup>h</sup>, Wade Watson<sup>i</sup>, Ron Olivenstein<sup>j</sup>, Anne Van Dam<sup>k</sup>, Cristina Villa-Roel<sup>l</sup>, and Roland Grad<sup>m</sup>

Assess potential reasons of poor control, and correct if indicated	Investigations
<p><b>Assess adherence</b></p> <p><b>Assess inhalation technique</b></p> <p><b>Assess environmental, including occupational, exposures</b></p> <p><b>Assess key potential co-morbidities or alternative diagnoses, and if suspected, investigate/treat</b></p> <p>Rhinosinusitis</p> <p>Gastro-esophageal reflux.</p> <p>Vocal cord dysfunction (VCD)</p> <p>Anxiety and depression</p> <p><b>Consider less frequent co-morbidities or alternative diagnosis</b></p> <p>Immunodeficiency</p> <p>Cystic fibrosis</p> <p>Tracheobronchomalacia or other suspected airway abnormalities</p> <p>Non CF bronchiectasis</p> <p>Vasculitis</p> <p>Allergic pulmonary aspergillosis</p> <p>Atypical mycobacteria infections</p>	<ul style="list-style-type: none"> <li>• Obtain drug dispensing record from pharmacy</li> <li>• Observe technique</li> <li>• Skin prick test to common aeroallergens, including aspergillus</li> <li>• Consider specific inhalation challenge with occupational agents to diagnose occupational asthma</li> </ul> <p>If unresponsive to medical therapy:</p> <ul style="list-style-type: none"> <li>• consider a CT scan of the sinuses.</li> <li>• 24-hour esophageal pH/manometry monitoring</li> <li>• If indicated, referral to an ENT surgeon with an interest in VCD</li> <li>• Psychological and/or psychiatric assessment</li> </ul> <ul style="list-style-type: none"> <li>• Immune work-up</li> <li>• Sweat chloride ± genetic testing for Cystic Fibrosis</li> <li>• Bronchoscopy</li> <li>• Chest CT Scan</li> <li>• Vasculitis screen</li> <li>• Aspergillus specific IgE, and if positive, precipitins</li> <li>• Sputum culture for atypical mycobacteria</li> </ul>



## **International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma**

Kian Fan Chung<sup>1,2,21</sup>, Sally E. Wenzel<sup>3,21</sup>, Jan L. Brozek<sup>4</sup>, Andrew Bush<sup>1,2</sup>, Mario Castro<sup>5</sup>, Peter J. Sterk<sup>6</sup>, Ian M. Adcock<sup>1</sup>, Eric D. Bateman<sup>7</sup>, Elisabeth H. Bel<sup>6</sup>, Eugene R. Bleecker<sup>8</sup>, Louis-Philippe Boulet<sup>9</sup>, Christopher Brightling<sup>10</sup>, Pascal Chanez<sup>11</sup>, Sven-Erik Dahlen<sup>12</sup>, Ratko Djukanovic<sup>13</sup>, Urs Frey<sup>14</sup>, Mina Gaga<sup>15</sup>, Peter Gibson<sup>16</sup>, Qutayba Hamid<sup>17</sup>, Nizar N. Jajour<sup>18</sup>, Thais Mauad<sup>19</sup>, Ronald L. Sorkness<sup>18</sup> and W. Gerald Teague<sup>20</sup>

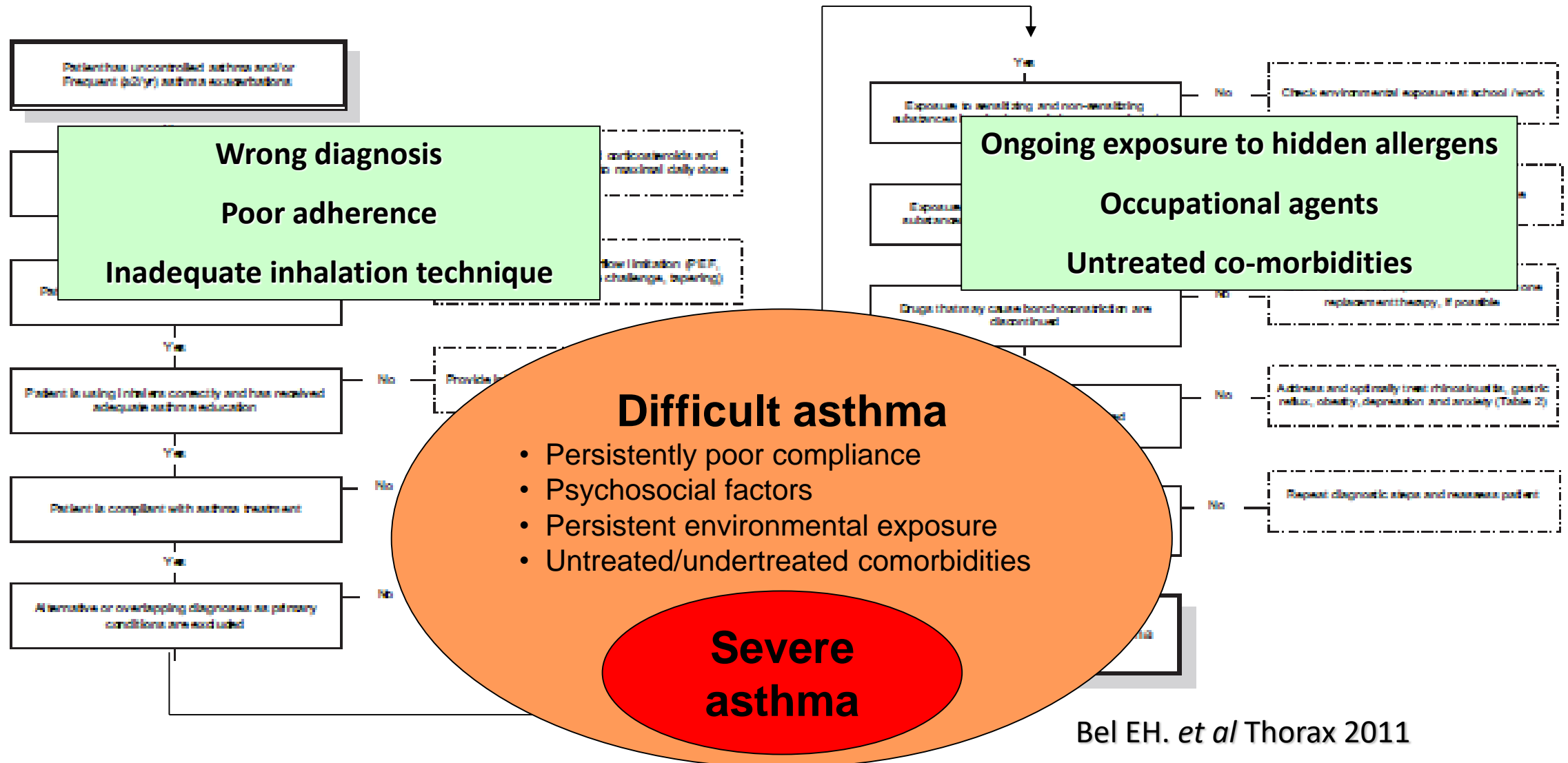
### ***Question 1***

Should chest HRCT scans be routinely ordered in patients with symptoms of severe asthma without known specific indications for performing this test (based on history, symptoms and/or results of other investigations)?

### ***Recommendation 1***

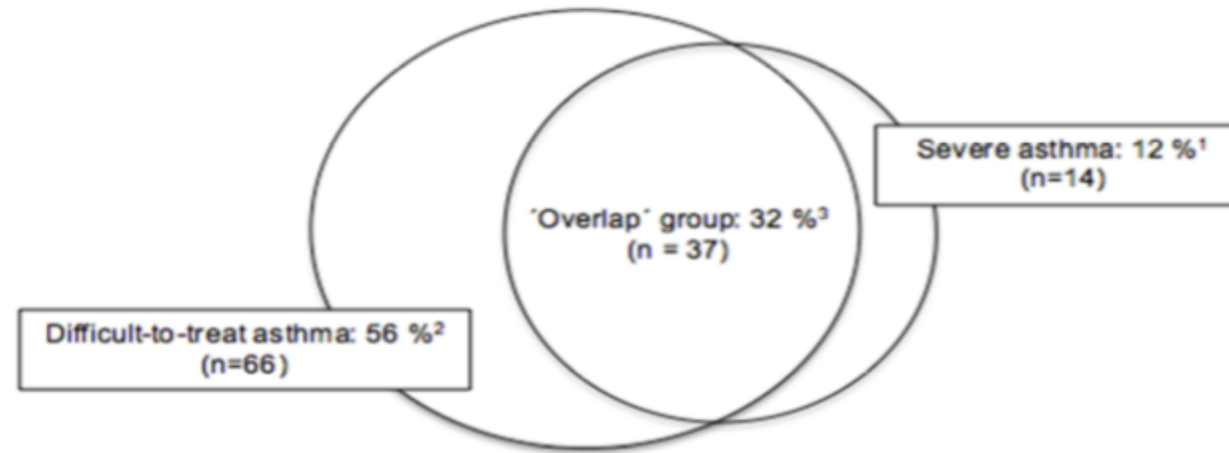
In children and adults with severe asthma without specific indications for chest HRCT based on history, symptoms and/or results of prior investigations we suggest that a chest HRCT only be done when the presentation is atypical (conditional recommendation, very low quality evidence).

# Checklist for evaluating patients with difficult-to-control asthma



# Differentiation of adult severe asthma from difficult-to-treat asthma – Outcomes of a systematic assessment protocol

Anna von Bülow, Vibeke Backer, Uffe Bodtger, Niels Ulrik Søes-Petersen, Susanne Vest, Ida Steffensen, Celeste Porsbjerg



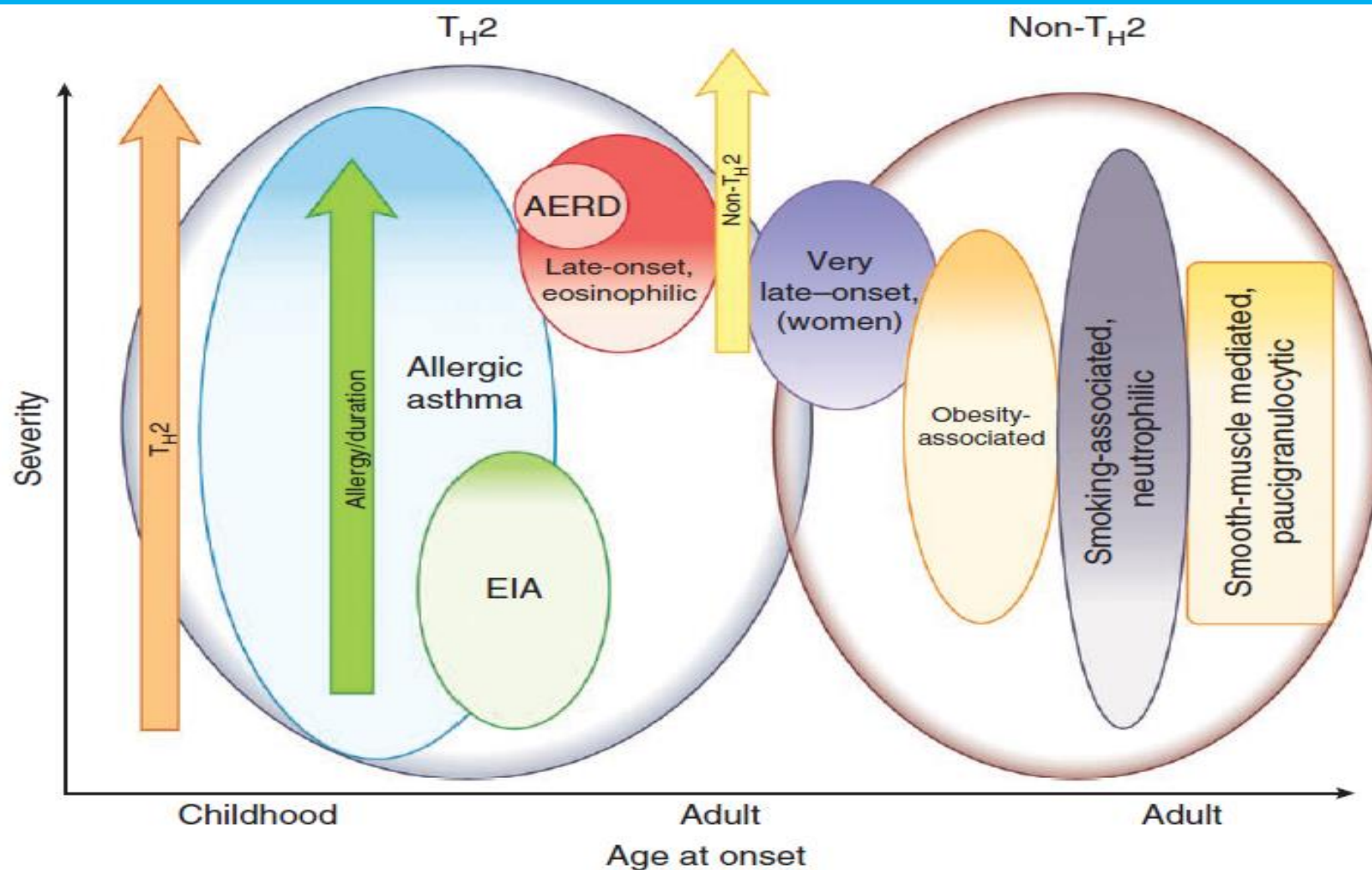
**Figure 2:** Distribution of patients with difficult-to-treat asthma and severe asthma after primary systematic assessment.

<sup>1</sup>Severe asthma: confirmed asthma diagnosis and adherence, inhaler technique, comorbidities and exposures being managed. <sup>2</sup>Difficult-to-treat asthma: Sub-optimal adherence or incorrect inhaler technique.

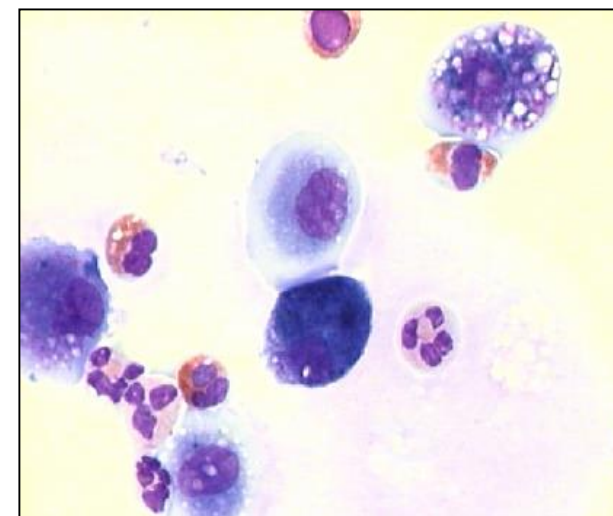
<sup>3</sup>“Overlap group” where patients potentially could belong into both groups: adherence  $\geq 80\%$ , no critical inhaler errors but at least one of the following: clinical asthma diagnosis (but no objective confirmation), unmanaged comorbidity (DB, obesity or untreated GERD, OSA (high risk), allergic persistent rhinitis, rhinosinuitis or anxiety/depression) or ongoing exposure (current smoking, allergen exposure combined with atopy or use of salicylates, NSAID or beta-blockers).



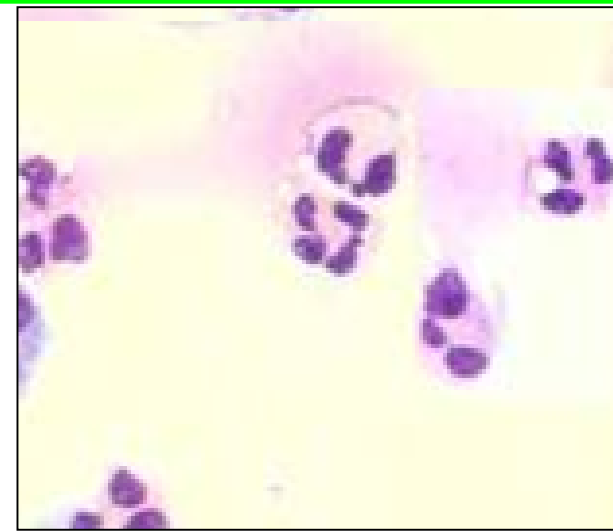
# Step 4 : Severe asthma phenotyping



Type 2: Eosinophilic inflammation



Non-Type 2: neutrophilic or pauci-granulocytic

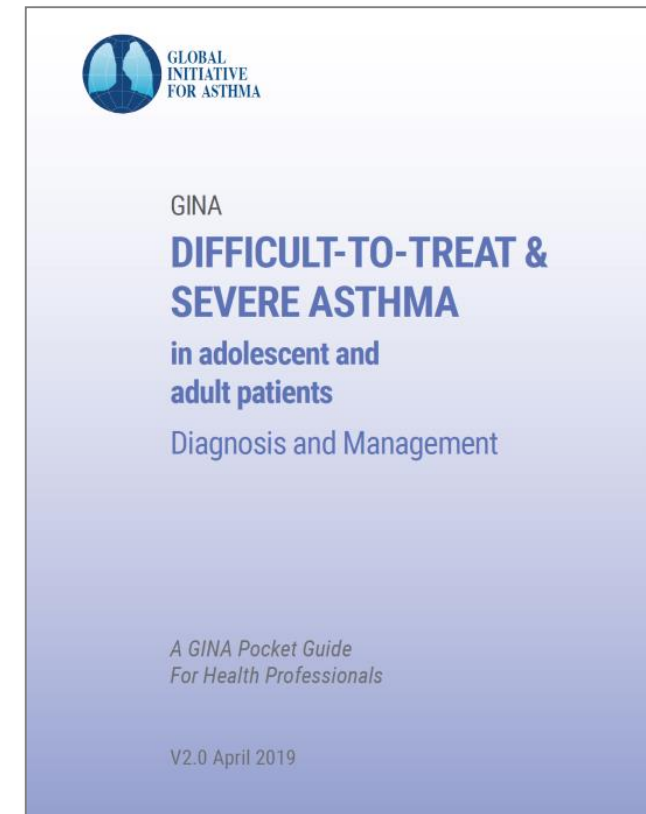




# Other changes in GINA 2019 – severe asthma



- 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 2019
  - 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



# Severe asthma decision tree: diagnosis and management

## Severe asthma decision tree: diagnosis and 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

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS:  
"Difficult-to-treat asthma"

**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



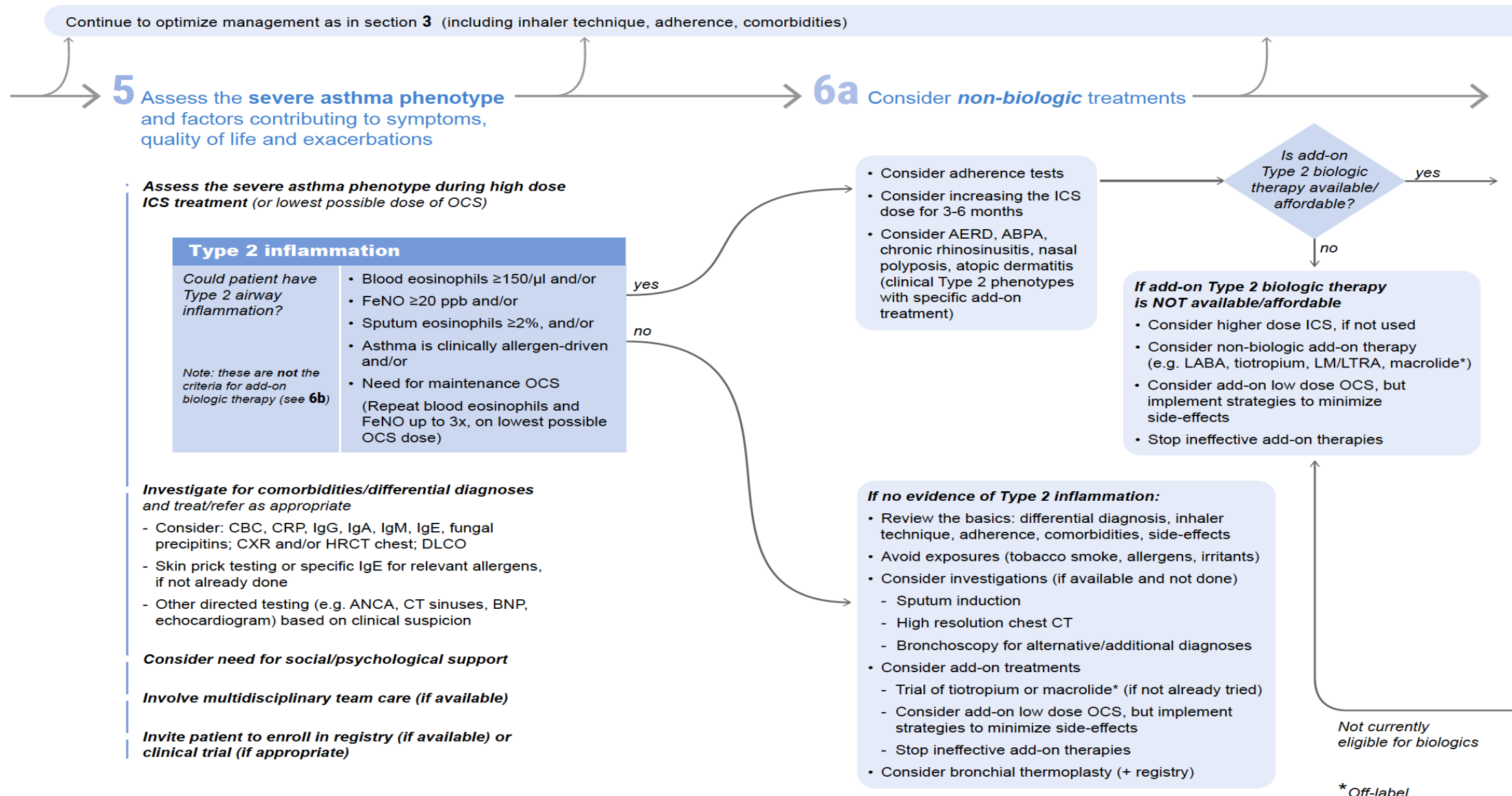
intervention, treatment



diagnosis, confirmation

For more details

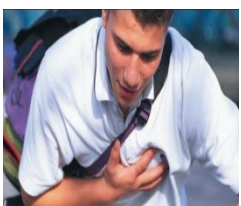
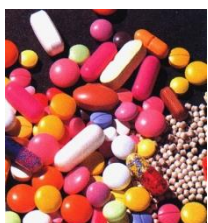
# Assess and treat severe asthma phenotypes



# A 1-day visit in a severe asthma center - Netherlands

- 47 patients with uncontrolled asthma (in 1 year)
  - 58.6% were adherent to treatment
  - In 9% the diagnosis of asthma could not be confirmed
  - 51% had severe asthma - 40% DTT asthma
  - Additional diagnoses contributing to poor asthma control in almost all patients (chronic rhinosinusitis and dysfunctional breathing being the most prevalent)
  - After the assessment, 83% of the patients returned to their own pulmonologist provided with a personalized management plan and only 7 patients remained for follow up in the severe asthma center (5 anti-interleukin 5 trial, 2 anti-IgE treatment)
- Demographics, medical history, BMI
  - Smoking
  - Comorbidities incl. psychological functioning and contributing factors
  - Adherence and inhalation technique
  - Peripheral blood cell counts
  - Atopic status (total and specific IgE to a panel of common aeroallergens)
  - Spirometry before and after B/D
  - Chest HRCT, sinuses and ear CT
  - 6-min walking distance (6MWD)
  - Airway inflammation (FeNO and cell differentials in induced sputum)

# An algorithm for the DTT asthma patient management



**Check Adherence/Persistence**

**Allergy Testing**  
**Avoidable Risk Factors**  
**Differential Diagnosis**  
**Comorbidities**

**Assessment of T2 markers**  
sputum cell counts  
FeNO  
blood eosinophils

**Referral to Specialist Center**  
(biologics, thermoplasty etc.)





