Recent Update of Bronchial Asthma Guideline

Severe Asthma

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

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GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

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improve overall symptoms and quality of life, decrease formation of nasal polyps and sinus infections, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores.[277]

Difficult-to-treat and severe asthma

Although the majority of patients can achieve the goal of well controlled asthma, some patients' asthma will not be well controlled even with optimal therapy.[95] The term *'difficult-to-treat' asthma* is used for patients in whom ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control. *'Treatment-resistant' or 'refractory' asthma* refers to patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remain poorly controlled despite high-dose ICS plus a second controller such as LABA (and/or systemic corticosteroids) and management of comorbidities, or whose asthma control deteriorates when this treatment is stepped down. *Severe asthma* includes patients with refractory asthma, and those in whom response to treatment of comorbidities is incomplete.[110]

Diagnosis

Factors that should be assessed and addressed in patients with uncontrolled asthma, before assuming that they have severe asthma, are shown in Box 2-4 (p22). Confirmation of the diagnosis is important, because in 12–50% of people assumed to have severe asthma, asthma is not found to be the correct diagnosis.[283] Strategies for confirming the diagnosis of asthma in patients already taking controller treatment are shown in Box 1-4 (p10).

Clinical features

Many people with severe or difficult-to-treat asthma experience frequent or persistent asthma symptoms, frequent exacerbations, persistent loss of lung function, substantial impairment of quality of life, and troublesome comorbidities such as anxiety and depression.[110,284] There is substantial heterogeneity in the clinical and inflammatory features of severe asthma, with several studies identifying clusters of patients with features such as early-onset severe allergic asthma; late onset non-atopic steroid-dependent asthma with fixed airways obstruction; and older obese women with late onset asthma.[5,6,126,283] To date, only a few specific targetable biological pathways have been identified,[7,133,134] but this is an area of active research.

Management

Referral of patients with severe asthma to a health care provider with expertise in asthma management may be helpful for investigation and treatment. Additional investigations that should be considered for patients suspected of having severe asthma, and additional therapies or strategies that may assist in their management, are shown in Box 3-14.

When potential reasons for a lack of treatment response have been considered and addressed, a compromise level of asthma control may need to be accepted and discussed with the patient to avoid futile over-treatment (with its attendant cost and potential side-effects) (Evidence D). The objective is then to minimize exacerbations and the need for emergency medical interventions while achieving as high a level of symptom control as is feasible.[110] This should be achieved with as little disruption of activities and as few daily symptoms and side-effects as possible. [110]

Box 3-14. Investigation and management of severe asthma

Investigations in severe asthma

- **Confirmation of the diagnosis of asthma**: upper airway dysfunction, concurrent COPD, and recurrent respiratory infections must be considered as alternative diagnoses or as contributors to persistent symptoms (Box 1-3, p8).[110]
- **Investigation for comorbidities**, including chronic sinusitis, obesity, GERD, obstructive sleep apnea and psychological or psychiatric disorders, that may worsen asthma control or contribute to symptoms. The ability to improve severe asthma by treating comorbidities remains unconfirmed (see *'Managing comorbidities'*, p47).[110]
- **Checking of inhaler technique and medication adherence**: incorrect inhaler use[71] and poor adherence[285] are the most common reasons for failure to achieve good asthma control (see Box 3-11 p42, Box 3-12 p44), and they are also found in severe asthma. In difficult-to-treat asthma, adherence and health outcomes may be improved with a comprehensive adherence-promoting intervention.[286]
- **Investigation for persistent environmental exposure to allergens or toxic substances**: these triggers, if present at home or workplace should be addressed and removed whenever possible (see Box 3-8 and Appendix Chapter 6).

Management of severe asthma

Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

- **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[287] (Evidence B). However, this carries the risk of systemic side-effects;[283] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p37) (Evidence D).
- **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[283] (Evidence D), but the potential long-term side-effects should be taken into account. Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[176]
- **Add-on treatments without phenotyping**: other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting anti-cholinergic bronchodilator, tiotropium*, showed improved lung function and decreased reliever use.[288]
- **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[130] (Evidence A).
- **Phenotype-guided add-on treatment**: patients with severe asthma may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[5,6,126,283] Patients with severe allergic asthma with elevated IgE levels may benefit from anti-IgE therapy[289] (Evidence A), and LTRAs may be helpful for patients found to be aspirin sensitive[280] (Evidence B).
- **Non-pharmacological interventions**: bronchial thermoplasty may be helpful in selected patients with severe asthma (Evidence B),[90] but more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations[110] (see Appendix Chapter 6). Carefully controlled trials are important as a large placebo effect has been seen in studies to date.[90] High-altitude treatment[283] (Evidence C) or psychological interventions[290] (Evidence C) may be helpful in patients with severe asthma. The place of these therapies and strategies in severe asthma has not been established.[110]

*This treatment does not appear in the recommendations in Box 3-5 as it has not yet been approved for asthma by a major regulator.

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3. Evaluation
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TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

1. Task Force Definition of Severe Asthma

Severe Asthma: Definition

- World Health Organization Consultation (2009)
  - three groups of severe asthma
  - untreated / difficult-to-treat / treatment-resistant

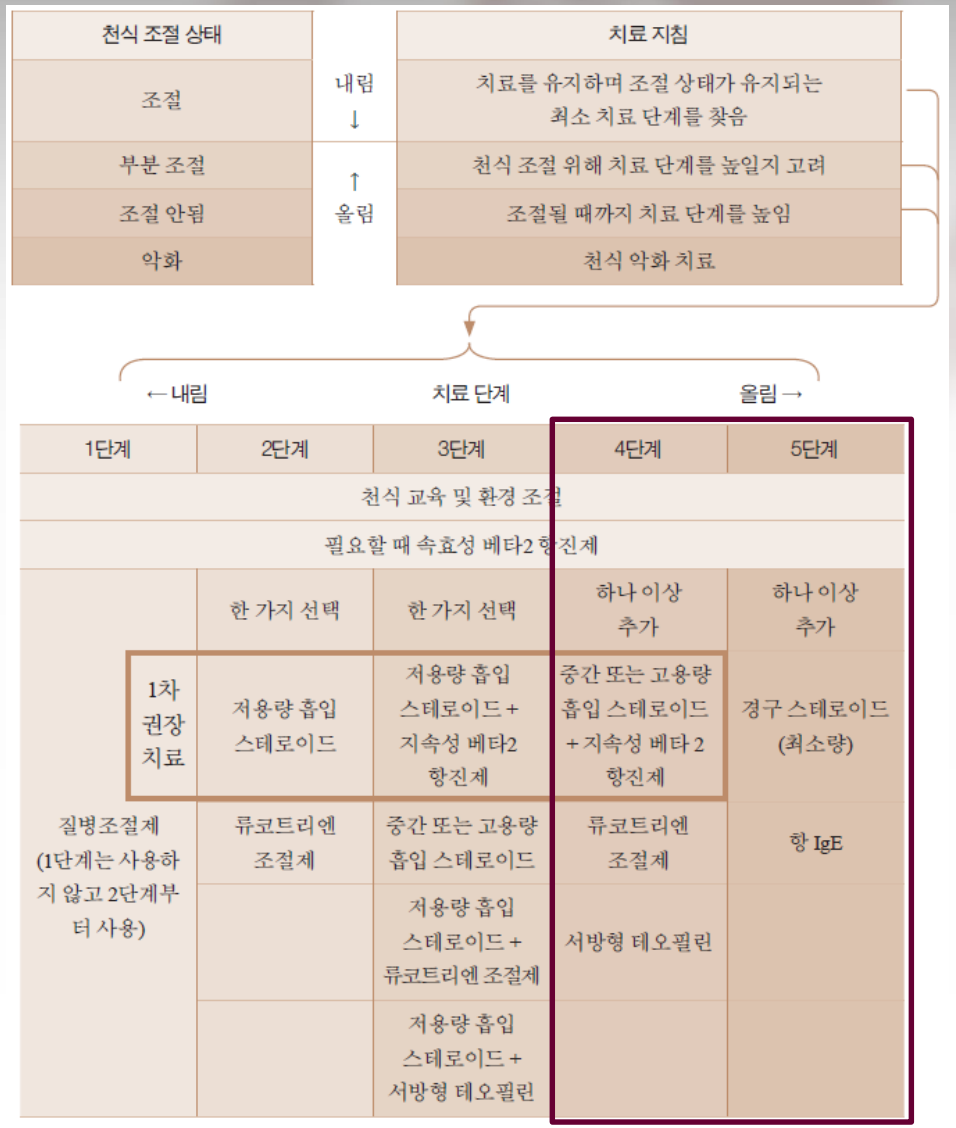
- European Respiratory Society (ERS), the American Thoracic Society (ATS), and panels of experts
  - Asthma that **requires high-intensity treatment** although modifiable factors and comorbidities have been appropriately managed

    (1) those who require continuous high-intensity treatment to maintain control

    (2) those with poor asthma control and/or frequent exacerbations despite high-intensity treatment

Severe Asthma: Definition

- ERS/ATS task force
  - ‘SEVERE ASTHMA’
  (1) Asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or
  (2) Asthma that remains uncontrolled despite this therapy.



천식 조절 상태		치료 지침
조절	내림 ↓	치료를 유지하며 조절 상태가 유지되는 최소 치료 단계를 찾음
부분 조절	↑ 올림	천식 조절 위해 치료 단계를 높일지 고려
조절 안됨		조절될 때까지 치료 단계를 높임
악화		천식 악화 치료

← 내림 치료 단계 올림 →

	1단계	2단계	3단계	4단계	5단계
천식 교육 및 환경 조절					
필요할 때 속효성 베타2 항진제					
		한 가지 선택	한 가지 선택	하나 이상 추가	하나 이상 추가
	1차 권장 치료	저용량 흡입 스테로이드	저용량 흡입 스테로이드 + 지속성 베타2 항진제	중간 또는 고용량 흡입 스테로이드 + 지속성 베타 2 항진제	경구 스테로이드 (최소량)
질병조절제 (1단계는 사용하지 않고 2단계부터 사용)		류코트리엔 조절제	중간 또는 고용량 흡입 스테로이드	류코트리엔 조절제	항 IgE
			저용량 흡입 스테로이드 + 류코트리엔 조절제	서방형 테오필린	
			저용량 흡입 스테로이드 + 서방형 테오필린		

Severe Asthma: Task Force Definition

Definition of Severe Asthma for Patients Aged ≥ 6 Years

Asthma requires

1) Medication for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year ***or***

2) systemic CS for ≥50% of the previous year

to prevent it from **becoming 'uncontrolled'** or which **remains 'uncontrolled'** despite this therapy

Severe Asthma: Task Force Definition

Definition of high daily dose of various inhaled corticosteroids in relation to patient age		
Inhaled corticosteroid	Threshold daily dose in μg considered as high	
	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	≥800 (DPI or CFC MDI)	≥2000 (DPI or CFC MDI)
	≥320 (HFA MDI)	≥1000 (HFA MDI)
Budesonide	≥800 (MDI or DPI)	≥1600 (MDI or DPI)
Ciclesonide	≥160 (HFA MDI)	≥320 (HFA MDI)
Fluticasone propionate	≥500 (HFA MDI or DPI)	≥1000 (HFA MDI or DPI)
Mometasone furoate	≥500 (DPI)	≥800 (DPI)
Triamcinolone acetonide	≥1200	≥2000

Severe Asthma: Task Force Definition

Definition of Severe Asthma for Patients Aged ≥ 6 Years

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control:
   - ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)

2) Frequent severe exacerbations:
   - Two or more bursts of systemic CS (>3 days each) in the previous year

3) Serious exacerbations:
   - At least one hospitalization, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation:
   - After appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma

: worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Severe Asthma: GINA 2014 Definition

- **Difficult-to-treat asthma**

  Patients in whom ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control.

- **Treatment resistant or Refractory asthma**

  Patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remained poorly controlled despite high dose ICS plus second controller such as LABA (and/or systemic CS) and management of comorbidities, or whose asthma control deteriorates when this treatment is stepped down.

- **Severe asthma**

  Patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.

Severe Asthma: Task Force Definition

- **Stage 1:**

  Confirm an asthma diagnosis and identify difficult-to-treat asthma

- **Stage 2:**

  Differentiate severe asthma from milder asthma

- **Stage 3:**

  Determine whether the severe asthma is controlled or uncontrolled

TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

2. Phenotyping:

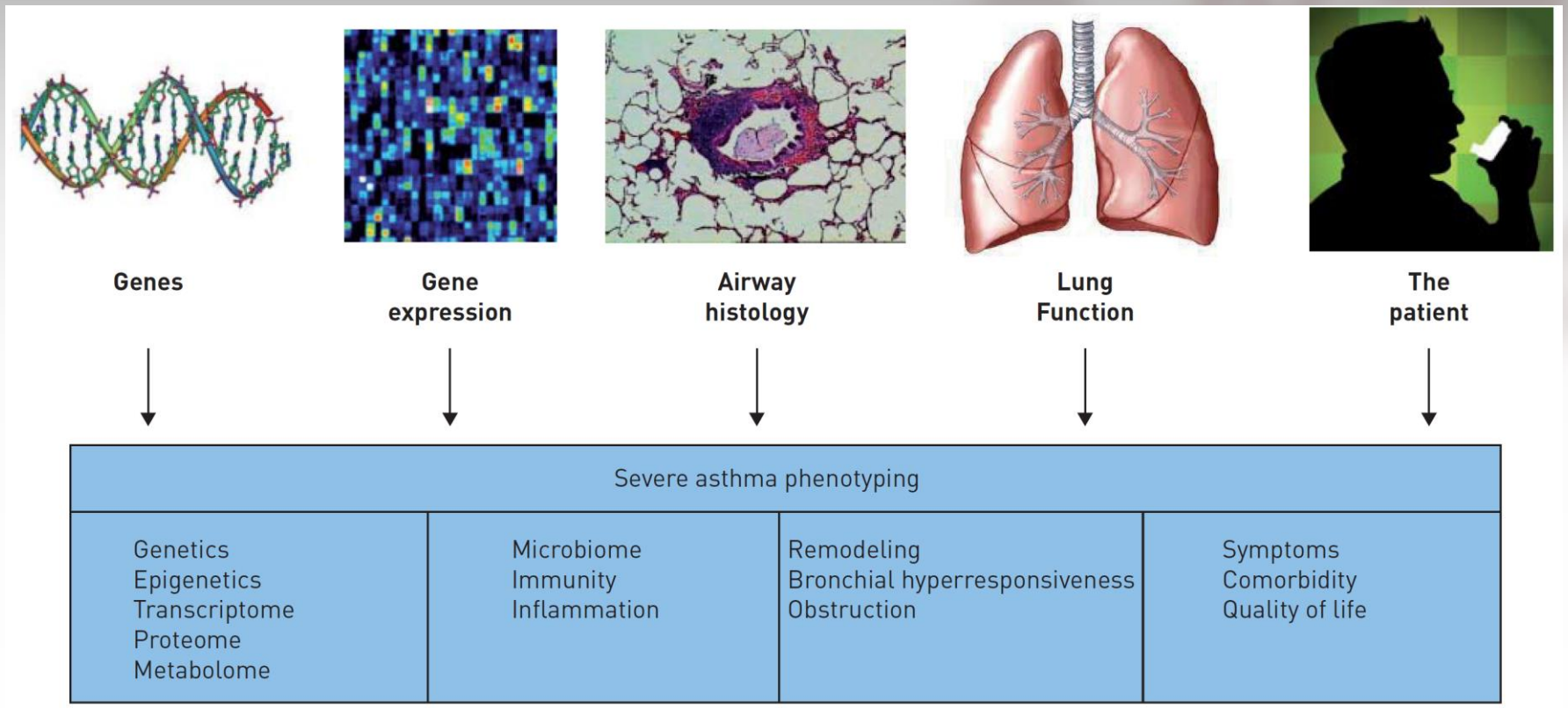
Epidemiology, Pathogenesis, Pathobiology, Structure and Physiology

Phenotyping: Phenotypes and clusters of severe asthma

- **Phenotypes**
  - Observational characteristics
  - Clinical, physiological, morphological, and biochemical characteristics and responses to different treatment

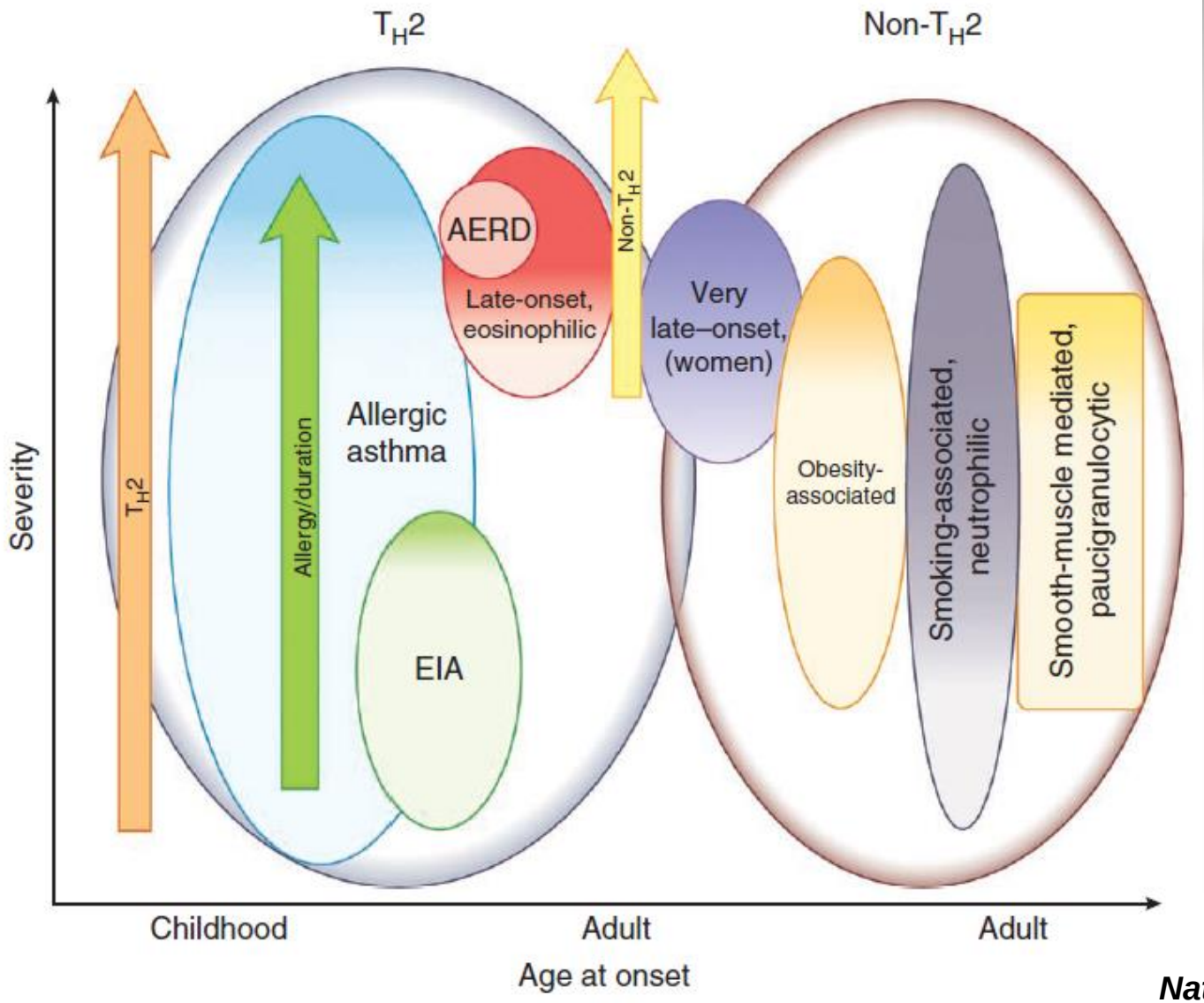
- **Endotypes**
  - Subtype of disease defined functionally and pathologically by molecular mechanism or by treatment response

Phenotyping: Phenotypes and clusters of severe asthma



- **FIGURE 1.** Integration of factors, beginning with genetics, which may contribute to the ultimate phenotype of the severe asthma patient.

Phenotyping: Phenotypes and clusters of severe asthma



- **Theoretical grouping of emerging asthma phenotypes based on the distinction between TH2-high asthma and non-TH2 asthma.**

Nature Medicine 2012;18:716-25

Study Authors	Population	Major Outcomes/Conclusions
Severe Asthma Research Program (SARP)		
Busacker et al, 2009	• 60 SA from SARP cohort • 34 MMA • 26 healthy controls	• **Air-trapping phenotype associated with asthma duration, history of pneumonia, airway neutrophilia, airflow obstruction, and atopy** • Quantitative CT-determined air trapping identifies asthma phenotype at **high risk for severe disease**
Moore et al, 2010	• 726 SA from SARP cohort	• Identification of five distinct clinical phenotypes using cluster analysis: **Cluster 1**: early-onset atopic asthma with normal lung function / **Cluster 2**: early-onset atopic asthma and preserved lung function but increased medication requirements and health care use / **Cluster 3**: mostly older obese women with late onset nonatopic asthma, moderate reductions in FEV1, and frequent oral CS use / **Cluster 4 and 5**: patients with severe airflow obstruction, frequent exacerbations, use of oral CS, history of ICU admission, and poor QoL
Hastie et al, 2010	• 242 SA from SARP cohort	• **Increased sputum eosinophils and neutrophils** associated with SA phenotype characterized by the lowest lung function, worse asthma control, and increased symptoms and health care requirements
Holguin et al, 2011	• 436 SA from SARP cohort • 613 MMA	• Patients with asthma are differentially affected by **obesity** based on whether they had early- or late-onset asthma • Obese subjects with early-onset asthma had more airway obstruction, AHR, and more oral CS courses or ICU admissions

Phenotyping: Natural history and risk factors

- **Early childhood-onset asthma:**
  - allergic sensitisation, a strong family history and, more recently, non-allergy/atopy related genetic factors.

- **Late-onset severe asthma:**
  - female sex and reduced pulmonary function despite shorter disease duration
  - persistent eosinophilic inflammation, nasal polyps and sinusitis and often aspirin sensitivity, and respiratory tract infections

Phenotyping: Genetics and epigenetics

- **Genetic approaches in complex diseases such as asthma can predict risk for development (susceptibility) or progression (severity).**
- Understanding the **functional biology of gene variants** may help identify biomarkers in relation to phenotypes and new pharmacotherapies.
  - single nucleotide polymorphisms in the interleukin (IL)-4 receptor-α
  - variation in IL-6 receptor
- Another mechanism predisposing to more severe or difficult-to-treat asthma may relate to **pharmacogenetics**

Phenotyping: *Inflammation and adaptive immunity*

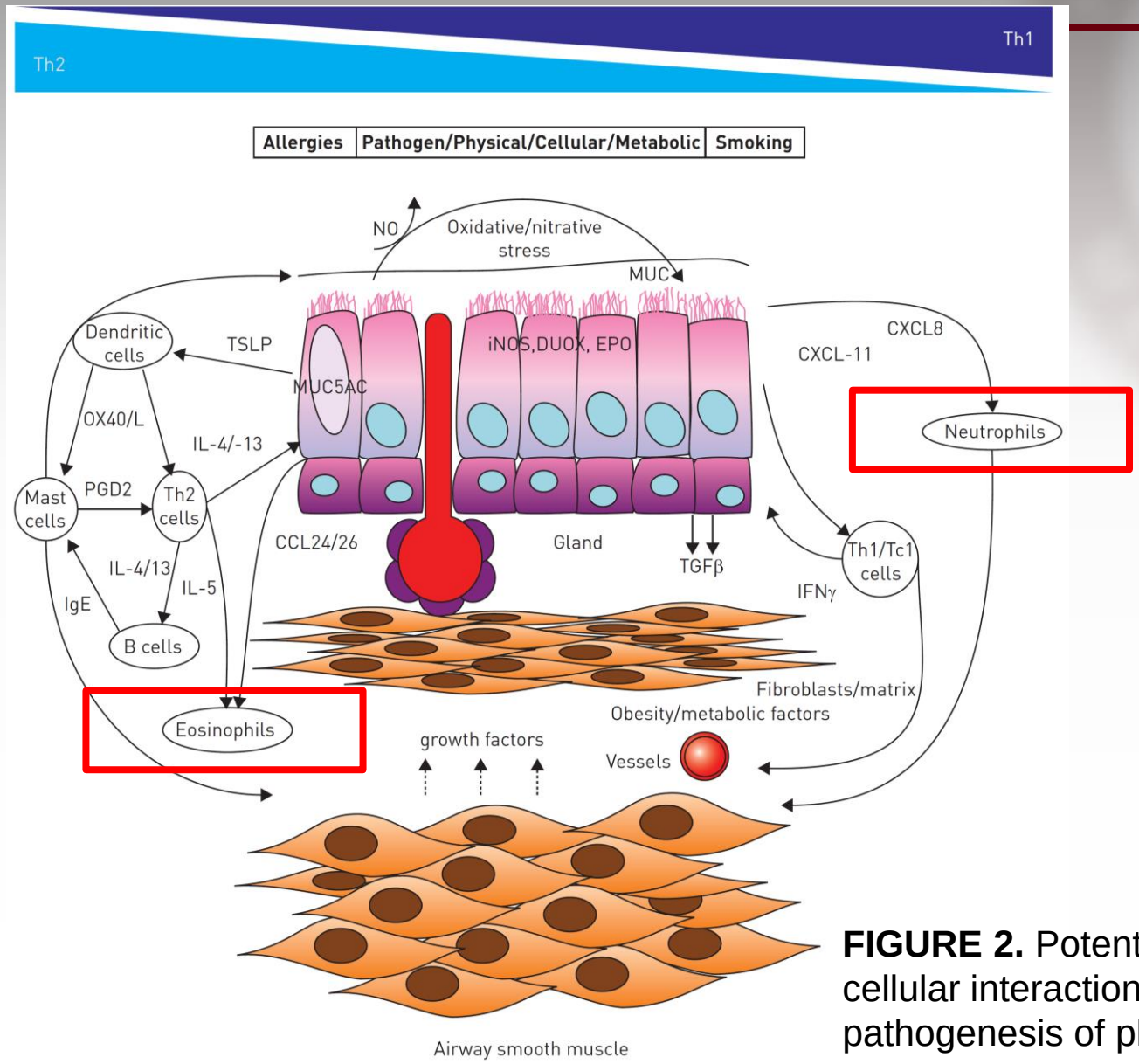


FIGURE 2. Potential immune-inflammatory and cellular interactions contributing to the pathogenesis of phenotypes of asthma.

Phenotyping: Respiratory infections

- The role of infections, particularly viral infections, in asthma exacerbations is well-established and their contribution to asthma development and progression increasingly recognized.

- **However, the relation to asthma severity has rarely been addressed.**

- These infection-related factors have only been evaluated in cross-sectional studies with modest regard to asthma characteristics or phenotypes
  - **fixed airflow limitation has been associated with positive serology for intracellular pathogens, such as Chlamydia pneumonia.**

Phenotyping: *Activation of innate immune pathways*

- There is growing evidence for involvement of innate immune pathways, with certain aspects abnormally diminished while others may be enhanced.
  - Impairment of macrophage phagocytosis of apoptotic epithelial cells or of bacteria
  - Impairment of TLR signaling
  - increased expression of thymic stromal lymphopoietin, IL-25 and IL-33 in airway cells
  - Increased oxidative and nitrative stress
  - Increased TNF-α expression

Phenotyping: *Structural abnormalities*

- Resident airway cells such as epithelial, fibroblast and smooth muscle cells are increasingly recognized as modulators of inflammation and remodeling.
- Structural alterations can affect airway mechanics, while structural cells can also contribute to inflammatory processes through release of cytokines, chemokines, growth factors and extracellular matrix elements.
  - Epithelium
  - Airway smooth muscle
  - Fibrocyte

Phenotyping: Physiology

- Chronic airflow limitation which is less responsive to bronchodilators and to inhaled or oral corticosteroid therapy is observed in some severe asthma phenotypes.
- Several prospective studies suggest that male sex, smoking, increased FeNO and African ancestry are contributors, while interestingly, allergic status may be protective.

Severe Asthma: Phenotypes

1. Clinical/physiology-Related Phenotypes
   a. Type and number of exacerbations
      - ✓ exacerbation-prone asthma
      - ✓ near-fatal asthma
   b. Pattern of airflow obstruction
      - ✓ fixed airway obstruction
      - ✓ small airway obstruction
   c. Presence of comorbidities
      - ✓ obesity-related asthma
      - ✓ asthma with rhinosinusitis

Severe Asthma: Phenotypes

2. Pathology/pathophysiology-related phenotypes
   a. Type of inflammation
      - ✓ eosinophilic
      - ✓ neutrophilic
      - ✓ paucigranulocytic
   b. Structural changes
      - ✓ remodeling
   c. Site of inflammation
      - ✓ large airways
      - ✓ small airways
   d. Smooth muscle abnormality

Severe Asthma: Phenotypes

3. Treatment-related phenotypes
   a. Corticosteroid responsiveness
      - ✓ corticosteroid-dependent asthma
      - ✓ corticosteroid-resistant asthma
   b. β-adrenergic responsiveness
   c. Immunomodulated treatment response
      - ✓ anti-IgE
      - ✓ anti–IL-5
   d. Inflammatory-based treatment
      - ✓ anti–IL-5
      - ✓ CXCR2
   e. Smooth muscle–targeted therapy
      - ✓ bronchial thermoplasty

Phenotyping: Conclusion

Priority questions on phenotypes

1) The validation of the **eosinophilic versus non-eosinophilic**, and of the **Th2 predominant versus non-Th2 asthma phenotype**, are they persistent over time and do they predict distinct natural histories?

2) Are **risk factors, comorbid factors and natural history** also governed by specific immune-inflammatory phenotypes?

3) Are there **genetic, epigenetic and inflammatory biomarkers** of specific phenotypes or characteristics of severe asthma?

4) Is the **innate immune response abnormal in severe asthma**, and do these contribute to inflammation and remodelling of the airways?

5) What is the relationship between **structural determinants, inflammation and airway function in severe asthma**, and can imaging be used to noninvasively address these issues?

6) Is there an altered **microbiome and virobiome** in the airways of severe asthma?

TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

3. Evaluation

Evaluation:

Step 1: Determining that the patient has asthma

- **Misdiagnosis** of non-asthmatic conditions as uncontrolled asthma has been reported to be **as high as 12–30%.**
- **Start with a careful history** with asthma symptoms, exacerbating triggers, and environmental or occupational factors.

Diseases which can masquerade as severe asthma (Adults)	
Dysfunctional breathlessness/vocal cord dysfunction	Hypereosinophilic syndromes
Chronic obstructive pulmonary disease	Pulmonary embolus
Hyperventilation with panic attacks	Herpetic tracheobronchitis
Bronchiolitis obliterans	Endobronchial lesion/foreign body (e.g. amyloid)
Congestive heart failure	Allergic bronchopulmonary aspergillosis
Adverse drug reaction (e.g. ACE inhibitors)	Acquired tracheobronchomalacia
Bronchiectasis/cystic fibrosis	Churg–Strauss syndrome
Hypersensitivity pneumonitis	

Evaluation:

Step 1: Determining that the patient has asthma

- **Confirmation of reversible airflow limitation**
  - spirometry with both inspiratory and expiratory loops, assessed following pre- and post-bronchodilator administration
- **Further testing** with **complete pulmonary function tests**, including diffusing capacity, and **bronchoprovocation testing** or **exercise challenges** can be considered.
  - particularly when there are inconsistencies between history, physical features and spirometry.

- Referral to a specialized center where patients can undergo a systematic evaluation, resulted **in 30–50% of patients previously called severe, being classed as difficult-to-control**.

Evaluation:

Step 1: Determining that the patient has asthma

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**).

Remarks

An atypical presentation of severe asthma includes such factors as, for example, **excessive mucus production, rapid decline in lung function, reduced carbon monoxide transfer factor coefficient and the absence of atopy in a child with difficult asthma**.

Evaluation:

Step 2: Assessing comorbidities and contributory factors

Comorbidities and contributory factors
1) Rhinosinusitis/(adults) nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety, depression
3) Vocal cord dysfunction
4) Obesity
5) Smoking/smoking related disease
6) Obstructive sleep apnea
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
9) Gastro-esophageal reflux disease (symptomatic)
10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), b-adrenergic blockers, angiotensin-converting enzyme inhibitors

Evaluation:

Step 3: Approaches to asthma phenotyping

- Currently, there are **no widely accepted definitions of specific asthma phenotypes**.
- However, identifying certain characteristics of certain phenotypes may eventually promote targeted and/or more effective therapies as well as help to predict different natural histories which may be of benefit to some patients.
- **Eosinophilic inflammation**, **allergic/Th2 processes** and **obesity** have been identified as characteristics or phenotypes which may be helpful when considering **nonspecific (corticosteroid) and specific (targeted) therapy (e.g. anti-IgE, anti-IL5 and anti-IL13 antibody treatments).**

TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

4. Therapy

Therapy: Using established asthma medication

1. Corticosteroid insensitivity

- ‘Corticosteroid insensitivity’ vs. ‘Corticosteroid resistance’
- Corticosteroid insensitivity has been associated with different comorbid conditions such as obesity, smoking, low vitamin D levels, and non-eosinophilic (low-Th2 inflammation) mainly in adults.
- In adults, a **non-eosinophilic phenotype** appears to form a large subgroup of asthma, with data from a mild-to-moderate cohort showing relatively poor corticosteroid sensitivity.
- Novel treatments such as p38 mitogen-activated protein kinase inhibitors and histone deacetylase-2 recruiters.
- Several agents with immunosuppressive properties, such as methotrexate, cyclosporin A, gold salts and i.v. IgG.

Therapy: Using established asthma medication

2. Inhaled and oral corticosteroid therapy

- **Control**
  - There is individual variation in the dose-therapeutic efficacy of ICS and some evidence that higher ICS doses may be more efficacious in severe asthma (including a systemic corticosteroid-sparing effect).
  - When standard medications are inadequate, OCSs are often added as maintenance therapy in severe asthma.
- **Exacerbation**
  - The optimal timing for initiation of OCS therapy has also not been defined.
  - Similarly, it is not yet clear whether continuous low-dose OCS are better than multiple discontinuous bursts for controlling exacerbations.
  - The use of sputum eosinophils and/or exhaled nitric oxide levels for guiding therapy in severe asthma remains controversial.

Therapy: Using established asthma medication

2. Inhaled and oral corticosteroid therapy

- **Systemic corticosteroid**
  - Use of continuous systemic corticosteroids should be accompanied by **prudent monitoring of weight, blood pressure, blood glucose, eyes and bone density** and, in children, appropriate growth.

Therapy: Using established asthma medication

3. Short- and long-acting β-adrenergic bronchodilators

- Step-wise increases in the dose of ICS, in combination with a LABA, improve the prospect of control compared with the use of ICS alone, including in some patients with severe asthma.
- Benefit of subcutaneous β-agonist in severe AE : not confirmed
- A strong association between the use of inhaled β-agonists and asthma mortality was reported with racial differences.
- Excessive use of β-agonists may be increased risk of β -agonist toxicity.
- Use of ipratropium bromide:
  - less effective, but well tolerated and may be used alternatively
- Routine use of Nebulizers:
  - discouraged
- Use of MDI with spacer:
  - as effective as s nebulizers

Therapy: Using established asthma medication

4. Slow-release theophylline

- In patients with moderate asthma, theophylline improved asthma control when added to ICS.
- In smoking asthmatics with corticosteroid insensitivity, theophylline with low dose ICS improved peak expiratory flow rates and asthma control.
- No such studies have been performed in children or adults with severe asthma.

Therapy: Using established asthma medication

5. Leukotriene pathway modifiers

- Montelukast is not as effective as LABAs when added to ICS therapy in preventing exacerbations requiring systemic corticosteroids or improving symptoms in moderate asthma.
- Addition of a leukotriene receptor antagonist or synthesis inhibitor has shown some efficacy on lung function when added to ICS in three studies of adults with moderate-to-severe asthma who were not taking LABAs.
  - Two of these studies were performed in aspirin-sensitive asthma
- Whether individuals with the **phenotype of aspirin-sensitive asthma** respond better than those without aspirin-sensitive asthma has not been formally addressed.

Therapy: Using established asthma medication

5. Long-acting muscarinic antagonists

- Tiotropium bromide improved lung function and symptoms in moderate-to-severe asthma patients not controlled on moderate- to high-dose ICSs with or without LABAs.

Therapy:

Specific approaches directed towards severe asthma

- Several clinical questions that are important to practicing clinicians in the management of patients with severe asthma

- The utility use of biomarkers to guide treatment
  - Sputum eosinophilia and/or FeNO.
- The therapeutic options
  - Anti-IgE therapy, methotrexate as a steroid-sparing agent, the use of macrolide therapy, the role of antifungal treatments, and the newer treatment of bronchial thermoplasty.

Therapy:

Currently available biomarkers to guide therapy

Question 2

Should treatment guided by sputum eosinophil count, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?

Recommendation 2

In adults with severe asthma, we suggest treatment guided by clinical criteria and sputum eosinophil counts performed in centers experienced in using this technique rather than by clinical criteria alone (conditional recommendation, very low quality evidence).
In children with severe asthma, we suggest treatment guided by clinical criteria alone rather than by clinical criteria and sputum eosinophil counts (**conditional recommendation, very low quality evidence**).

Remarks
Patients who are likely to benefit from this approach are those who can **produce sputum, demonstrate persistent or at least intermittent eosinophilia and have severe asthma with frequent exacerbations.**

Therapy:

Currently available biomarkers to guide therapy

Question 3

Should treatment guided by FeNO in addition to clinical criteria, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?

Recommendation 3

We suggest that clinicians do not use FeNO to guide therapy in adults or children with severe asthma (**conditional recommendation, very low quality evidence**).

Therapy:

Currently available biomarkers to guide therapy

Question 4

Should a monoclonal anti-IgE antibody be used in patients with severe allergic asthma?

Recommendation 4

In patients with severe allergic asthma we suggest a therapeutic trial of omalizumab both in adults (**conditional recommendation, low quality evidence**) and in children (conditional recommendation, very low quality evidence).

Remarks

Adults and children (aged ≥6 years) with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance, if their total serum IgE level is 30–700 IU/mL.

Therapy:

Currently available biomarkers to guide therapy

Question 5

Should methotrexate be used in the treatment of severe asthma?

Recommendation 5

We suggest that clinicians do not use methotrexate in adults or children with severe asthma (**conditional recommendation, low quality evidence**).

Remarks

Because of the probable adverse effects of methotrexate and need for monitoring therapy we suggest that any use of methotrexate is limited to specialized centers and **only in patients who require daily OCS**.

Therapy:

Currently available biomarkers to guide therapy

Question 6

Should macrolide antibiotics be used in patients with severe asthma?

Recommendation 6

We suggest that clinicians do not use macrolide antibiotics in adults and children with severe asthma for the treatment of asthma (**conditional recommendation, very low quality evidence**).

Therapy:

Currently available biomarkers to guide therapy

Question 7

Should antifungal agents be used in patients with severe asthma?

Recommendation 7

We suggest antifungal agents in adults with severe asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA) **(conditional recommendation, very low quality evidence**).

We suggest that clinicians do not use antifungal agents for the treatment of asthma in adults and children with severe asthma without ABPA irrespective of sensitisation to fungi (i.e. positive skin prick test or fungus-specific IgE in serum) (**conditional recommendation, very low quality evidence**).

Therapy:

Currently available biomarkers to guide therapy

Question 8

Should bronchial thermoplasty be used in patients with severe asthma?

Recommendation 8

We recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study (**strong recommendation, very low quality evidence**).

Therapy:

New experimental molecular-based treatments for severe asthma

Placebo-controlled studies of potential new treatments in severe asthma

First author	Severity	Subjects n	Design	Treatment	Outcomes	Summary results
WENZEL	Severe	309	R, db, pc, p	Golimumab, anti TNF-a, 24 weeks	FEV1, AE, AQLQ, PEFR	FEV1 unchanged, no reduction in AE, AQLQ, PEFR Adverse profile side-effects
PAVORD	Severe, with ≥ 2 AEs in past year	621	R, db, pc, p	Mepolizumab (75, 250 or 750 mg infusions at 4 weeks), anti-IL-5, 52 weeks	Rate of AEs	All doses reduced AEs by 39–52%, No effect on ACQ, AQLQ or FEV1
HALDAR	Severe	61	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	AEs, symptoms, FEV1, AQLQ, AHR, sputum and blood Eosinophils	Reduced Aes Improved AQLQ Reduced eosinophils
NAIR	Severe	20	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	AEs, oral steroid reduction	Reduced exacerbations, eosinophils and OCS dose
KIPS	Severe	26	R, db, pc, p	SCH55700, anti-IL-5, 12 weeks	Sputum and blood eosinophils, symptoms, FEV1	Reduced blood sputum eosinophils No other significant outcomes
CASTRO	Poorly controlled on high-dose inhaled CS	53	R, db, pc, p	Reslimuzab, anti-IL-5, 12 weeks	ACQ, FEV1, Sputum eosinophils	Improved ACQ score Reduction in sputum eosinophils Improved FEV1

Therapy:

New experimental molecular-based treatments for severe asthma

Placebo-controlled studies of potential new treatments in severe asthma

First author	Severity	Subjects n	Design	Treatment	Outcomes	Summary results
CORREN	Moderate-severe	294	R, db, pc, p	AMG317, anti-IL-4Ra antibody, blocks IL-4 and IL-13, 12 weeks	ACQ scores, AEs	No effect on ACQ or AEs
CORREN	Moderate-severe	219	R, db, pc, p	Lebrikizumab, anti-IL13 antibody, 24 weeks	Change in prebronchodilator FEV1	Improved FEV1, compared with placebo, with greatest changes in high levels of periostin or FeNO group (post hoc analyses) No effect on ACQ-5 or diary measures. AEs were 60% lower in treated group with high Th2
PIPER	Moderate-tosevere	194	R, db, pc, p	Tralokinumab (150, 300, or 600 mg), IL-13 neutralising monoclonal antibody, 3 months	Change from baseline in ACQ-6 at week 13	No change in ACQ-6 at 13 weeks FEV1 increase of 0.21 L versus 0.06 L with placebo (p=0.072). b2-agonist use decrease of -0.68 versus -0.10 with placebo (p=0.020). Better response in those with higher IL-13 levels in sputum

Therapy:

New experimental molecular-based treatments for severe asthma

Placebo-controlled studies of potential new treatments in severe asthma

First author	Severity	Subjects n	Design	Treatment	Outcomes	Summary results
HUMBERT	Severe, CS-dependent	44	R, db, pc, p	Masitinib (3, 4.5 and 6 mg·kg-1·day-1), c-kit and PDGFR tyrosine kinase inhibitor, 16 weeks	OCS dose ACQ, FEV1	No difference in OCS dose ACQ improved, no difference in FEV1
BUSSE	Moderate-to-severe		R, db, pc, p	Daclizumab, IL-2Ra chain antibody, 20 weeks	Change in FEV1 (%) Asthma AEs	Improved FEV1 Reduction in day-time asthma scores, use of SABA Prolonged time to severe AEs. Reduction in blood eosinophils
NAIR	Severe asthma	34	R, db, pc, p	SCH527123, CXCR2 receptor antagonist, 4 weeks	Changes in sputum and neutrophil activation markers	Reduction in blood and sputum neutrophil Reduction in mild exacerbations No reduction in ACQ score (p=0.053)

Therapy:

New experimental molecular-based treatments for severe asthma

Potential Phenotype-Targeted Therapies in Severe Asthma

Characteristic	Associations	Specifically Targeted Treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High FeNO	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High FeNO	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

SUMMARY

- **Investigations in severe asthma**
  - ✓ Confirmation of the diagnosis of asthma
  - ✓ Investigation for comorbidities
  - ✓ Checking of inhaler technique and medication adherence
  - ✓ Investigation for persistent environmental exposure to allergen or toxic substances
- **Management of severe asthma**
  - ✓ ICS remain the mainstay of therapy
  - ✓ Optimization of ICS/LABA dose
  - ✓ Oral corticosteroids
  - ✓ Add-on treatments without phenotyping: Tiotropium
  - ✓ Phenotype-guided add-on treatment

THANK YOU for YOUR ATTENTION