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EUFOREA pocket guide on the diagnosis and management of asthma: An educational and practical tool for general practitioners, non-respiratory physicians, paramedics and patients

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To the editor,

International and national initiatives on asthma management provide extensive information on asthma pathophysiology, offering expert guidance on diagnosis and recommendations on treatment, highlighting contemporary therapeutic options [1–3]. Likewise, there are several high-impact task force articles and expert reviews on related topics, including asthma exacerbations, treatable traits, comorbid conditions, biomarkers, biologics and corticosteroids [4–12]. However, the majority of these articles are very comprehensive and require profound background knowledge, and hence, are mainly suitable for experts in the field of respiratory medicine. In contrast, there is a lack of concise and practical information on asthma for non-specialists, including general practitioners (GPs), nurse-practitioners, paramedics and pharmacists, who see these patients in the first instance.

In line with the previously well-received concept of pocket guides on allergic rhinitis (AR) [13,14] and chronic rhinosinusitis (CRS) [15], the asthma expert panel of the European Forum for Research & Education in Allergy & Airway Diseases (EUFOREA), in collaboration with several global key opinion leaders in the field of chronic inflammatory airways disease, developed a pocket guide on asthma [16] largely based on international recommendations [1–3] complemented by professional experience. The overall aim of this guide is to provide a concise summary of the cornerstones of asthma diagnosis and management and, thus, to promote awareness, educate and support non-specialist stakeholders and patients.

To this end, the guide provides listings and tables of common manifestations and triggers of asthma, a summary of the key differential diagnoses, commonly encountered treatable traits and comorbid conditions, which should be proactively explored and addressed [Table 1]. Furthermore, we included a shortlist of essential diagnostic tools: *i.e.* guidance on lung function tests and assessment of airway inflammation which facilitate subtyping (phenotyping, endotyping) of individual patients leading to more personalized approach to management [Table 2; Table 3]. All these features are implemented in simple and clinically applicable algorithms: one specifically linking asthma diagnosis to management [Fig. 1], while the second one focuses on asthma management in the first (GP) and second (respiratory specialist) line of care [Fig. 2].

Patient awareness and education

Apart from chronic use at high doses, even infrequent short bursts of systemic corticosteroids (SCS) are associated with an increased risk of potentially serious side effects [17,18]. These include osteoporosis, fractures, ocular disorders (glaucoma, cataracts), skin bruising, gastro-intestinal bleeding, infections, metabolic syndrome, including diabetes, obesity and cardiovascular disease. In a recent publication, these steroid-induced health issues have been collectively referred to as ‘‘people remodeling’’ [19]. Therefore, patient awareness and education on the chronicity of the disease, preventive (lifestyle) measures, in combination with adequate inhaler technique and intake of controller treatment (or, cf updated GINA2023: maintenance or inhaled corticosteroids (ICS)-containing treatment [1]) are crucial for an optimized asthma control and to avoid sequelae of ‘‘people remodeling’’ associated with the intake of SCS as well as with frequent asthma exacerbations.

Inhaled corticosteroids: cornerstones of asthma treatment

Inhaled corticosteroids remain the cornerstone of asthma treatment even in patients with very mild disease with infrequent symptoms [1]. In this respect, the updated GINA2023 has issued two new terminologies, i.e. ‘‘***AIR***’’ and ‘‘***MART***’’, to reflect the dual purpose of the so-termed ‘anti-inflammatory reliever’ (AIR) consisting of as-needed ICS-formoterol and the recently added as-needed ICS-SABA, and the so-termed ‘maintenance and reliever therapy’ (MART). The AIR-only approach is recommended for treatment Steps 1–2, while the MART strategy is recommended for Steps 3–5 for adolescents (≥12 years) and adults. While in these steps the combination ICS-formoterol may serve as AIR on top of the MART, ICS-SABA combinations are not recommended as part of a MART regimen.

Biologics and allergen-immunotherapy – expert referral

Although most asthma patients can reach a satisfactory level of disease control, a distinct group with more severe disease, after assuring adherence and inhalation technique, will require re-evaluation to confirm the diagnosis of asthma, explore treatable traits and comorbidities, assess environmental factors and triggers and to perform additional tests, including inflammometry, *i.e.* simple tests if available in routine clinical practice [Table 2]. At this level, specialist referral or initiation of the next treatment step by a specialist or a multidisciplinary team may be required [Fig. 1; Fig. 2]. In our pocket guide, we provide a shortlist of indications for referral to an asthma expert which may differ (slightly) across countries.

Depending on the clinical and immunological profile (type (T)2 or non-T2) as well as on local availability, eligible patients may be prescribed biologics. Presently, most biologics target type2-inflammatory components (omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab) while the recently registered tezepelumab seems to demonstrate efficacy in both T2- and non-T2 asthma [9,20]. Patients

with allergen-driven disease should be considered for allergen immunotherapy (AIT, specifically sublingual immunotherapy (SLIT) tablets) in early stages [1,3,21]. Switching between biologics, and/or concomitant application of several biologic therapies may be needed in some patients [22].

Close disease monitoring and patient engagement

Close monitoring of several disease manifestations, including evaluation of asthma control, risk of exacerbations and/or side effects, comorbidities and treatable traits, as well as lung function, combined with re-evaluation of patient's expectations and satisfaction remain pivotal aspects of asthma management [Fig. 1; Fig. 2].

Disclaimer

As a consequence of the concise lay-out, and despite input from international experts, we are aware that this initiative also comes with several limitations and hence does not (fully) replace ongoing and new concepts or (inter)national recommendations and guidelines - which are subject to quick turnover upon emerging evidence or new insights and/or local preferences as well as the availability of health care resources. Soon after the launch of the EUFOREA pocket guide, GINA2023 was issued online and consequently, some of the latest concepts have not (yet) been fully implemented. EUFOREA aims to present updated versions of the pocket guides online on a regular basis.

Table 1
Key lung function tests in GP and specialist care [16].

Lung function testing

Although asthma may present with normal lung function or initial irreversible airway flow obstruction, confirmation of a variable lung function is usually part of asthma diagnosis. Variability may be demonstrated either spontaneously or through pharmacological intervention (reversibility test) or upon bronchoprovocation (inducing bronchoconstriction by pharmacological or physiological stimuli).

Confirmation of variable Lung Function

Ambulatory tests

- **PEF spontaneous variability** (diurnal variation measured over 7 days: ≥10% on average)
- **PEF variability to stimuli** (e.g. exercise or occupational stimuli: ≥15%)
- **PEF reversibility** ≥20% 15 mins after 2-4 puffs of SABA

Laboratory tests

- Reversibility of FEV1 or FVC to SABA (≥12% and 200mL)
- Reactivity to direct or indirect stimuli:
- Methacholine/histamine (PC20 or PD20)
- Mannitol (PC15 or PD15)
- Exercise or cold, dry air (≥15% fall from baseline FEV1)

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

PC: Provocative Concentration

PD: Provocative Dose

PEF: peak expiratory flow

SABA= Short-acting beta2 agonist

Authors credit statement

Conceptualization: ZD and LB have **conceived and developed** the EUFOREA asthma pocket guide with **extensive input** by the asthma expert panel: MJ, SQ, LH, RD, NH, DR, IP, VB, MG. GKS, DR and RD performed linguistic corrections. EvS skilfully crafted the format of the tables and figures. **Resources**: Funding acquisition by PH, ZD, LB., **Writing**: ZD wrote the manuscript with input from LB and approval from all co-authors., All authors have contributed in several aspects to the **development and/or review** of the EUFOREA asthma pocket guide and all approved this manuscript.

Declaration of competing interest

ZD: received consultancy fees/lecture fees/fees for attending advisory boards from ALK, Antabio, Foresee Pharmaceuticals, GlaxoSmithKline, Hippo-Dx, QPS-Netherlands, Sanofi-Genzyme; she served as Director Respiratory & Allergy at QPS-NL and this CRO received research grants for clinical trials from HAL Allergy, Janssen Research & Development LLC, Patara pharma, Cerbios, Merck Sharp & Dohme, Novartis, Foresee Pharmaceuticals and ERA4TB (IMI-project). **MJ:** ALK, Stallergenes-Greer, Chiesi, GSK, Pfizer, Novartis, AstraZeneca and SANOFI. **NH:** Received honoraria for serving as advisor or consultant for GSK, AstraZeneca, Sanofi, Regeneron, Amgen, Genentech, Novartis and Teva. His institution received research grant support of his behalf from GSK, Genentech, Sanofi, Teva, Novartis, and AstraZeneca. **LH:** Has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/ Genentech Inc, and Glaxo Smith Kline, Amgen, Genentech/Hoffman la Roche, Astra Zeneca, MedImmune, Glaxo Smith Kline, Aerocrine and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen. **RD:** Declares consulting fees from Synairgen, Sanofi and Galapagos, lecture fees from GSK, AZ and Airways Vista and he holds shares from Synairgen. **DR**: No COIs related to this work. **SQ:** ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GSK, Leti, Mundipharma, Novartis, Sanofi-Genzyme, Teva. **VB:** Has worked as advisor, supervisor, investigator of pharmaceutical studies, unrestricted grants, and others with: AstraZeneca, GSK, MSD & Shering Plough, ALK-Abello; Chiesi, Novartis, Pharmaxis, Pfizer, Boehringer Ingelheim, Aerocrine, Teva, Sanofi, Birk NPC as. **MG:** No COIs related to this work. **IP:** In the last 5 years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK and

Table 2
Asthma pheno-/endotyping and point-of-care inflammometric tests [16].

Asthma subtypes & Inflammometry

Currently **two major asthma subtypes** have been defined based on underlying immunological/inflammatory mechanisms:

- Type2 (or T2-high) and
- non-Type2 (or T2-low) asthma

Type 2 asthma is common and if early onset, usually presents with either allergy with or without prominent eosinophilia or, if late onset, with non-allergic eosinophilic inflammation.

Non-type2 asthma is still less well defined; with currently no available targeted biologic treatments.

Type 2 asthma is associated with:

- High risk of exacerbations and accelerated lung function decline
- High occurrence of CRSwNP
- T2-inflammation which can manifest as:
  - Allergic (positive allergy test and related symptoms)
  - Blood eosinophilia (≥300 cells//μL); (≥150 cells/μL if on SCS)
  - Fractional exhaled nitric oxide (FeNO) ≥25 ppb
- Good response to corticosteroids
- Good response to T2-targeted biologics (severe T2 asthma)

Inflammometry allows **subtyping (pheno/endotyping)** of individual patients, to **predict responsiveness to standard of care** (ICS) and/or **T2-targeted treatment options** (specialist care). FeNO may also serve as a check on adherence.

Currently applicable point-of-care biomarkers*):

- Skin prick test (SPT) ≥3 mm (mean perpendicular diameter) and/or
- Serum total and allergen-specific IgE (dependent on local laboratory)
- Blood eosinophils (≥300 cells/μL) (≥150 cells/μL if on SCS)
- FeNO (≥25 ppb)

*) *SPT, blood eosinophils and FeNO may normalize with systemic (oral) corticosteroids (SCS/OCS).*

Blood eosinophils and FeNO levels are highly variable and require repeated (≥3) measurements on different days.

ICS: inhaled corticosteroids

OCS: oral corticosteroids

SCS: systemic corticosteroids

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Table 3
Linking treatable traits to diagnostic tests/markers and treatment options [16].

Pulmonary domain	Marker/Parameter	Treatment/Action
Airflow limitation/airway hyperresponsiveness	Spirometry (FEV1 <80% of predicted value; FEV1/FVC <0.75)	Add LABA (+/-) LAMA to ICS; bronchial thermoplasty*
	Reversibility to SABA ≥12%+200mL	ICS + LABA
	Bronchoprovocation testing*)	see p 11
Small airways disease (SAD):	Spirometry (FEF25-75); plethysmography; MBW; IOS; imaging; CalvNO*)	Small particle inhalers; inhalation chamber; systemic treatment
Emphysema / COPD	Chest CT scan; DLCO, lung compliance measurement*)	Smoking cessation
Recurrent respiratory infections/mucus hyperproduction	Sputum culture	Antibiotics; long term low-dose macrolides*
Bronchiectasis (Common cause of recurrent respiratory infections)	Chest CT scan*)	Drainage; mannitol/ saline inhalations; nebulized bronchodilators; macrolides*
Airway inflammation/biomarkers (p 13)		
Eosinophilic:	Blood eosinophils ≥300 cells/ µL (≥150 cells/µL if on SCS)	Inhaled corticosteroids; (short course of OCS); biologics*
Type 2 inflammation:	FeNO ≥ 25 ppb	Inhaled corticosteroids; (short course of OCS); biologics*

Extrapulmonary domain	Marker/Parameter	Treatment/Action
Allergic rhinitis	Allergy test (skin/serum); relationship symptoms and exposure	Avoidance; antihistamines; nasal CS; AIT*; **
CRSwNP/CRSsNP	Nasal endoscopy/CT scan*)	Saline irrigations/nasal CS/ OCS; surgery; biologics*;**
AERD/NERD	Blood eosinophilia; history of aspirin/NSAIDs intolerance; CRSwNP	Avoidance; desensitisation*); ICS/OCS/LTRA; biologics*
Obesity	BMI, body composition	Refer to dietitian; physical activity; exercise, surgery*
OSA	Apnoea screen, Apnoea index, nocturnal desaturations	CPAP
GERD	Gastrointestinal endoscopy, oesophageal 24h pH-test*	Proton pump inhibitors; lifestyle adjustment*
Psychological factors (depression/anxiety/ stress)	Questionnaires; psychological/psychiatrist assessment*	Psychotherapy; pharmacotherapy*

Lifestyle /behavioral factors	Marker/Parameter	Treatment/Action
Intentional and unintentional non-adherence	Patient history; FeNO suppression with monitored therapy; prescription refill rate; smartinhalers	Education; discuss economic factors; frequent assessment of technique; smart inhalers; self-management support
Inadequate inhaler technique	Observed inhalation	Education; frequent assessment of technique; smart inhalers
Smoking/vaping/ exposure to noxious chemicals	Patient history; cotinine test	Smoking cessation; improve ventilation

*) in specialist setting/initiated by specialist

**) see EUFOREA pocket guides on AR/CRS

AIT: allergen immunotherapy

CalvNO: alveolar fraction of exhaled NO

CPAP: continous positive airway pressure

CRSwNP: chronic rhinosinusitis with nasal polyps

CS: corticosteroids

DLCO: diffusing lung capacity for carbon monoxide

FeNO: fractional exhaled nitric oxide

FEV1: forced expiratory volume in 1 second

FEV1/FVC: Tiffeneau-Pinelli index

FVC: Forced vital capacity

GERD: gastroesophageal reflux disease

ICS: inhaled corticosteroids

LABA: long-acting beta2-agonists

LTRA: leukotriene receptor antagonists

MBW: multiple breath washout

OCS: oral corticosteroids

OSA: obstructive sleep apnea

SABA: short-acting beta2 agonists

SCS: systemic corticosteroids

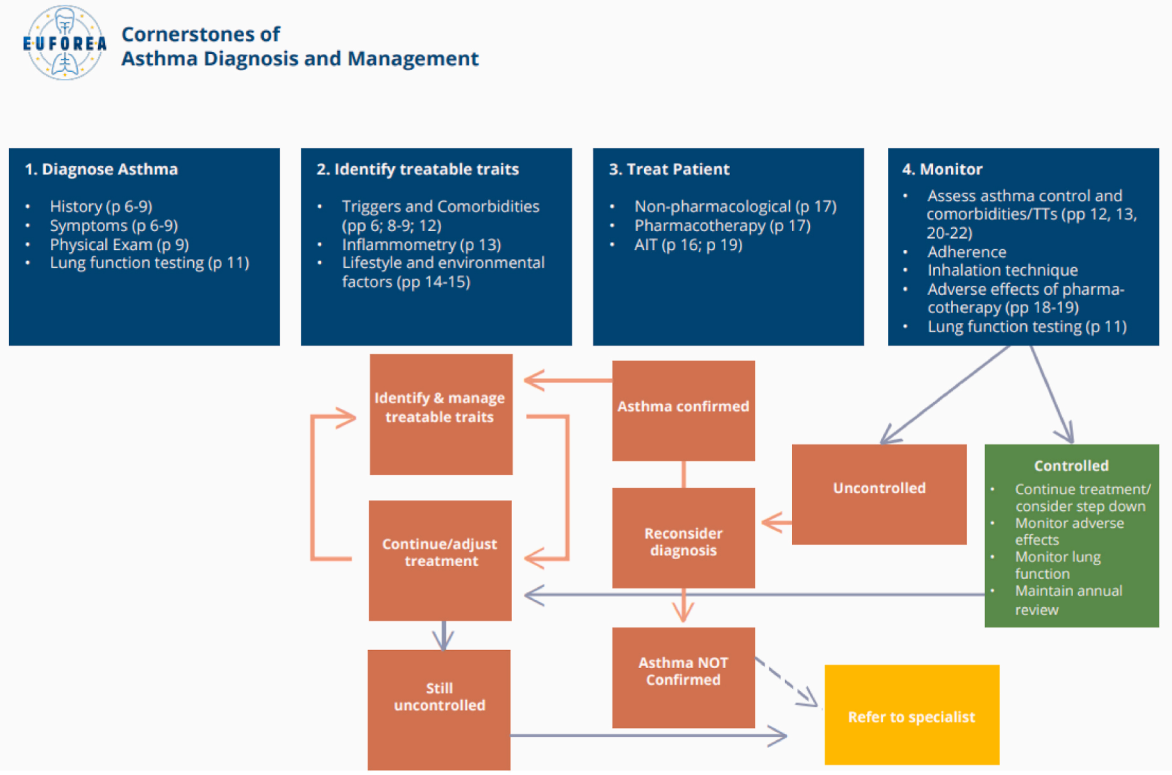

Fig. 1. Algorithm linking cornerstones of asthma diagnosis and treatment [16].

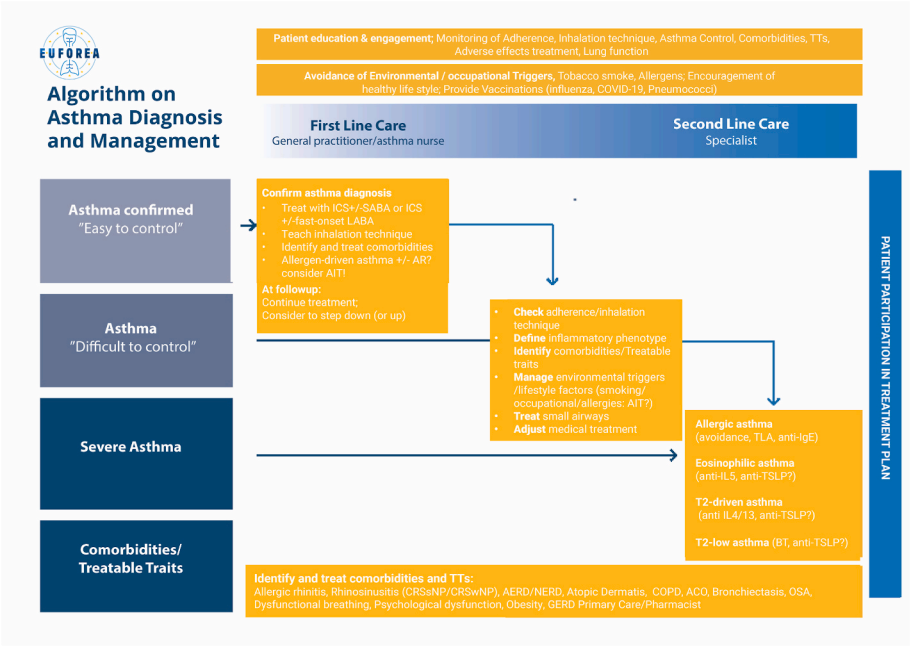

Fig. 2. Treatment algorithm for asthma (≥12 years) for the first and second line care [16].
ACO: asthma COPD overlap.
AIT: allergen immunotherapy.
AR: allergic rhinitis.
COPD: chronic obstructive pulmonary disease.
BT: bronchial thermoplasty.
ICS: inhaled corticosteroids.
LABA: long-acting beta2 agonists.
LAMA: long-acting muscarinic antagonists.
OSA: obstructive sleep apnea.
SABA: short-acting beta2 agonists.
TLA: temperature-controlled laminar airflow.
TT: treatable traits.

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