RESEARCH ARTICLE

Recommendations for severe asthma management from a Gulf Cooperation Council expert panel aiming to optimize regional clinical practice

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1. Background

Uncontrolled asthma, also termed severe asthma, is associated with significant morbidity and mortality and a high economic burden.[1] Despite the availability of numerous therapies targeted at controlling symptoms and preventing exacerbations,[2,3] levels of asthma control remain variably high across the globe, with population-based studies reporting control rates of 67% in Europe[4] and 55% in the USA.[5]

Data from the Middle East revealed that 44.2% of patients have uncontrolled asthma, which results in a greater frequency of healthcare services utilization, lower quality of life (QoL), and higher impact on daily activities compared with controlled asthma.[6] Many factors are thought to contribute to uncontrolled disease in the Gulf region in particular, including poor access to healthcare, limited patient and physician education, lack of appropriate follow-up, and low treatment adaptation.[6] Collectively, this highlights an unmet need requiring increased awareness and guidance on best practices for management.[7]

To this aim, a group of 12 experts practicing across the Gulf region herein provide recommendations for the management of severe asthma based on best available evidence and real-life experience from their daily practice; the overall objective was to optimize and standardize clinical practice in the region and improve patient outcomes.

2. Phenotype and biomarkers

As our understanding of asthma evolves, patient management and asthma outcomes continue to improve. In the past, patients with similar observable clinical characteristics were grouped and treated similarly; however, many failed to respond or achieve disease control with therapies considered to be standard of care.[8]

The heterogeneity of asthma, and severe asthma in particular, has driven the identification and use of biomarkers that can help in the classification of patients into distinct phenotypes and endotypes, and in the prediction and assessment of response to therapy.[9] A diagram representing the severe asthma phenotypes observed in the Gulf region based on our experience is shown in **Figure 1**.

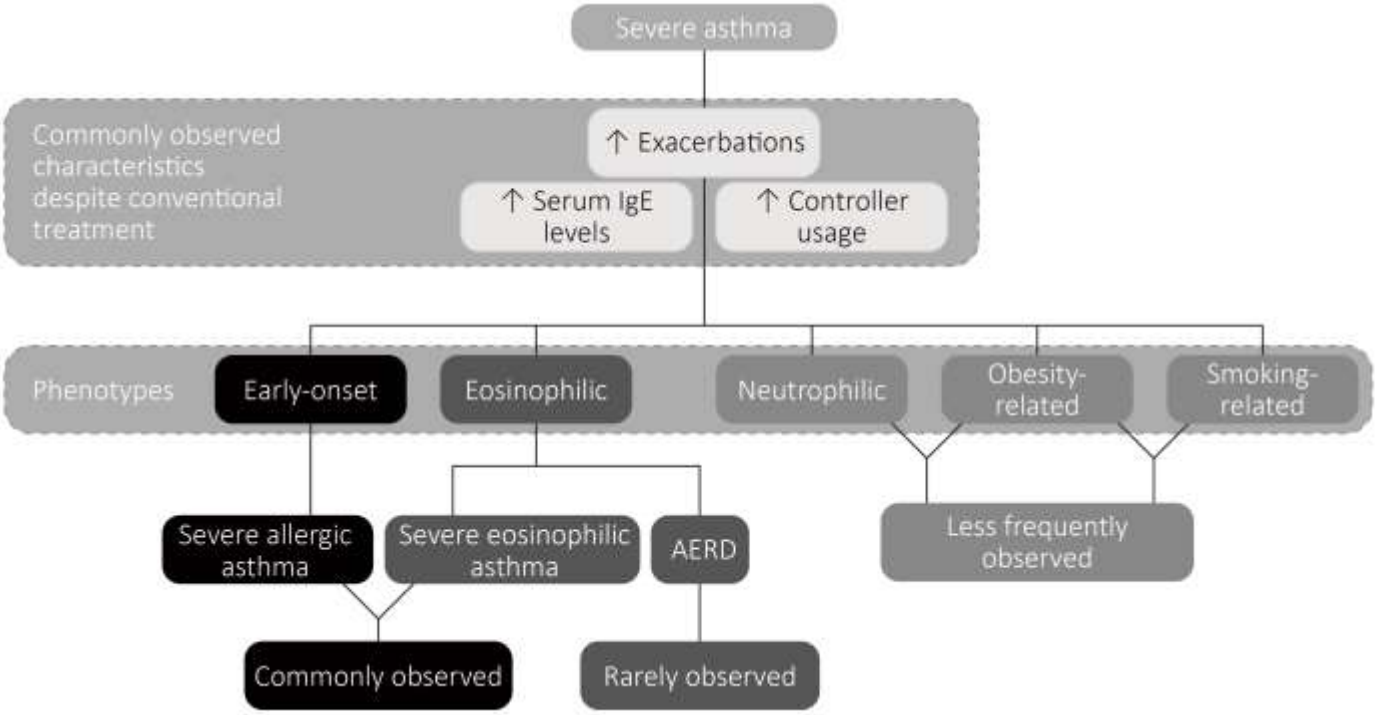

Figure 1 A schematic representation of severe asthma phenotypes in the Gulf region. Allergic asthma is the most prominent asthma phenotype.[1] *AERD,* aspirin-exacerbated respiratory disease.

At present, available biomarkers are focused on type 2 asthma and include blood and sputum eosinophils, immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), and serum periostin.[10] In our practice, total and specific IgE levels and eosinophil counts are assessed to determine severe asthma phenotype and biologic treatment in patients with severe allergic asthma (SAA). In patients with severe eosinophilic asthma (SEA), eosinophil counts (part of complete blood count [CBC]) and IgE levels are assessed, along with skin prick tests (if required) and C-reactive protein (CRP). In the AERD phenotype, total and specific IgE (including IgE for aspirin), eosinophil count, skin prick test (if required), and FeNO are evaluated. While we do not use specific biomarkers to assess the neutrophilic, smoking-related, and obesity-related phenotypes, CRP, CBC, skin prick test, and total IgE are used infrequently to assess these phenotypes. The radioallergosorbent test and/or antinuclear antibody test are also sometimes used before initiating treatment in patients with severe asthma.

Recommendation 1: The percentage of eosinophils and absolute eosinophil count should be assessed as these measurements not only aid in determining asthma phenotypes, they may also be of value in predicting response to treatment and might consequently guide therapy and follow-up.

Recommendation 2: Total and specific IgE levels should be assessed before initiation of anti-IgE

treatment; however, IgE levels cannot be used to guide follow-up treatment.

Recommendation 3: FeNO levels could be a good tool during follow-up and monitoring of asthma. Although FeNO testing is commercially available, it is not widely used in clinical practice, and its role in guiding therapy has not yet been well established.

Recommendation 4: Serum periostin as a biomarker in asthma is not currently available for use in routine clinical practice; however, it may be useful to assess the response to anti-interleukin (IL)-13 therapy in the future.

3. Treatment

Allergen avoidance is an integral part of asthma management. House dust mites (HDMs) are prevalent aeroallergens; therefore, sublingual and subcutaneous immunotherapy with HDM vaccines are used to desensitize patients with HDM allergic asthma, with good clinical response observed particularly in monosensitized individuals.

Severe asthma, consisting of the distinct phenotypes and endotypes proposed above, could be treated with several biologic therapies targeting T-helper cell type 2 (Th2) inflammation, predominantly characterized by type 2 cytokines such as IL-4, IL-5, IL-13, and IgE.[11] The heterogeneity in treatment response has inspired discussions around a precision approach to care that tailors treatment to the individual patient.[8]

In our practice, omalizumab is the treatment of choice for patients with SAA (irrespective of eosinophil count) given its excellent decade-long experience in terms of reduction in exacerbations and severity of asthma and improvement in asthma control, QoL, and patient satisfaction. Furthermore, the STELLAIR study has demonstrated the effectiveness of omalizumab in patients with SAA irrespective of pre-treatment blood eosinophil count.[12, 13] For patients with SEA, mepolizumab is the treatment of choice, and although treatment outcomes have been promising, clinical experience is limited as it was recently introduced to the market. Half of the experts in this work do not use any biologic therapy for AERD; inhaled corticosteroids (ICSs)/long-acting beta-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), montelukast, leukotriene receptor antagonists, theophylline (to a lesser extent), and aspirin desensitization are used to treat this group of patients instead. The other half prescribe omalizumab or mepolizumab. In patients with neutrophilic asthma, the use of biologic agents is limited, and treatment includes ICSs/LABAs, LAMAs, theophylline, montelukast, macrolides, and azithromycin (low dose). For patients with obesity- and smoking-related asthma phenotypes, counseling for weight reduction and bariatric surgery, and referral to smoking cessation clinics, respectively, are generally prescribed. If the obesity-related phenotype is associated with obstructive sleep apnea (OSA), then continuous positive airway pressure could be helpful. Furthermore, screening for OSA must be performed as part of the obesity-related phenotype assessment, as obesity rates are alarmingly high in the Gulf region.[14] A treatment algorithm for

selecting appropriate first-line biologic therapy is outlined in **Figure 2**.

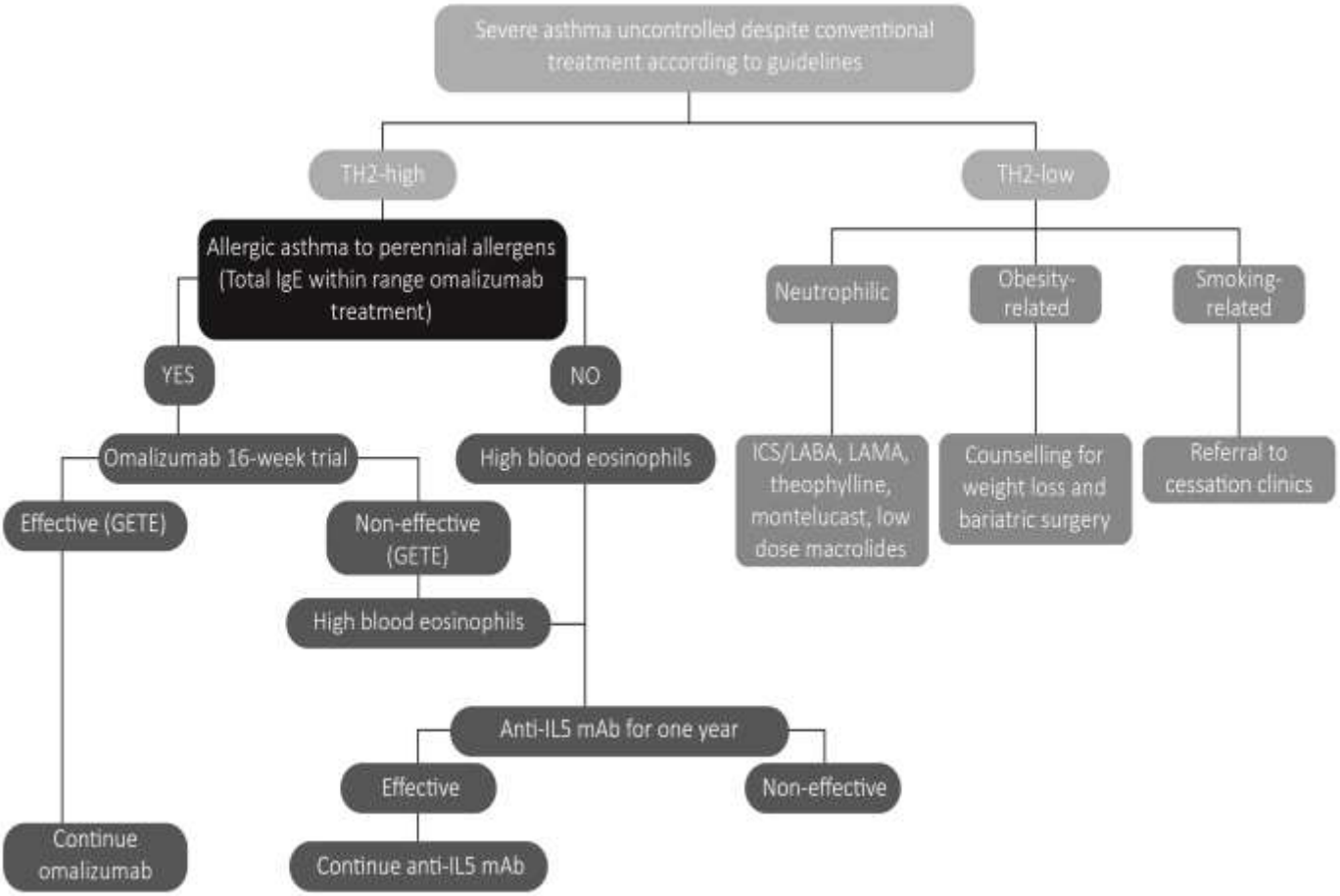

Figure 2 Proposed treatment algorithm for patients with severe asthma in the Gulf region. As a first step, eosinophils should be tested along with IgE levels. Based on our clinical experience across the Gulf region and global guidelines, initiating treatment with anti-IgE agents is warranted in patients with a documented history of allergy. The proposed algorithm may need to be revised in the near future, when regional real-world experience and clinical trial evidence on anti-IL-5 agents becomes available. *General note*: For children aged 6–<12 years who meet the prescribing criteria, omalizumab is the only approved biologic treatment.[15] *GETE,* Global Evaluation of Treatment Effectiveness; *mAb,* monoclonal antibody.

4. Conclusions

The heterogeneity of asthma, particularly severe asthma, has led to the identification of biomarkers and the development of biologic therapies targeted at specific phenotypes and endotypes. Nevertheless, despite the availability and growing repertoire of therapies to treat severe asthma, uncertainties and variability exist in selecting the appropriate therapy for the individual patient. Herein, we have proposed an algorithm for the treatment of severe asthma in the Gulf region, based on our experience and supported by best available evidence. Such an algorithm would need to be regularly updated given the rapidly evolving

therapies for asthma. Further research to better delineate the different phenotypes in patients with overlapping features is also needed to better individualize treatment and optimize outcomes.

List of abbreviations

AERD, aspirin-exacerbated respiratory disease; CBC, complete blood count; CRP, C-reactive protein; FeNO, fractional exhaled nitric oxide; GETE, Global Evaluation of Treatment Effectiveness; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mAb, monoclonal antibody; OSA, obstructive sleep apnea; QoL, quality of life; SAA, severe allergic asthma; SEA, severe eosinophilic asthma; Th2, T-helper cell type 2.

Declaration

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

BM, AA, MSA, MA, NHA, MWD, SA, FA, NHN, AMK, and AAE declare that they have no competing interests. MS is a medical associate of Novartis Middle East, Dubai, UAE.

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Author contributions

BM outlined and drafted the manuscript. BM, AA, MSA, MA, NHA, MWD, SA, FA, NSN, AMK, AAE, and MS contributed to the development of the recommendations and critically reviewed the manuscript. BM, AA, MSA, MA, NHA, MWD, SA, FA, NSN, AMK, AAE, and MS reviewed and revised the manuscript. All authors have approved the submitted version of the manuscript and have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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