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# Severe asthma: Entering an era of new concepts and emerging therapies: Highlights of the 4th international severe asthma forum, Madrid, 2018

To the Editor,

In the past decades, new insights into molecular mechanisms of severe asthma have further unveiled its heterogeneous nature prompting the need for personalised and targeted approaches. These and several other hot topics related to severe asthma were addressed in the 4th International Severe Asthma Forum, organized by the Asthma, ENT, Immunology and Pediatric sections of the European Academy of Allergy and Clinical Immunology in collaboration with the Spanish Society for Allergy and Clinical Immunology.

Severe asthma is currently defined as asthma that requires treatment with high-dose inhaled corticosteroids combined with a second controller ± systemic corticosteroids to maintain control or, asthma that remains "uncontrolled" despite this therapy.[1] While severe asthma affects 5%-10% of the entire asthma population, it accounts for >80% of the total healthcare costs related to asthma. Of note, severe asthma should be distinguished from difficult-to-treat asthma for which (re) evaluation of diagnosis, precipitating triggers, treatment adherence, as well as treatment of comorbidities is recommended. To improve treatment adherence, patient education on sustained use of controller medications in combination with a proper inhalation technique is mandatory. eHealth, comprising of a variety of tools and applications, including mobile devices (mHealth), can support patient awareness, improve adherence and support disease self-management.[2]

Sensitizing agents at the workplace can cause occupational asthma. Irritants are often related to work-exacerbated asthma but at high concentrations may also elicit occupational asthma. A detailed occupational history including the insight into potential sensitizers at work is an integral, but often under-emphasized, part of the evaluation of patient with severe asthma. Patients with occupational asthma due to high-molecular-weight (HMW) agents commonly present with rhinitis, conjunctivitis, atopy and early asthmatic reactions following specific inhalation challenge, while asthma exacerbations are more frequently associated with occupational asthma induced by low-molecular-weight (LMW) agents. Interestingly, the inflammatory profile triggered by HMW and LMW agents is similar.[3]

As for comorbidities, chronic rhinosinusitis with nasal polyps is a prevalent upper airway comorbidity in severe asthma, responding to corticosteroids and type 2 immune response (T2)-targeted therapies. Likewise, obesity, a key component of the metabolic syndrome, is linked to severe asthma. Asthma patients with metabolic syndrome experience worse respiratory symptoms resulting from both lung function impairment and increased airway inflammation. Obviously, proper advice on dietary intake, lifestyle adjustments and/or bariatric surgery should be part of severe asthma management.

Bronchiectasis is present in approximately 30% of patients with severe asthma. Although both diseases share overlapping features, such as symptoms, neutrophilic inflammation and airway hyperresponsiveness, common underlying pathways require further research.

Furthermore, a significantly higher prevalence of mental disorders, especially depression and anxiety, has been reported in patients with severe asthma. Patients with psychological comorbidities often present with low treatment adherence, smoking, inactivity and obesity. Hence, for severe asthma, psychological support is recommended as part of daily clinical practice.

Coinciding with a reduced response to standard treatment, severe asthma patients are often exposed to an overload of (combinations of nasal, cutaneous, inhaled and oral) corticosteroids causing adverse events which impose substantial healthcare costs. This clearly underscores the need for alternative treatment options enabling reduction of the overall corticosteroid dose.

Reflecting its heterogeneous nature, severe asthma comprises several different phenotypes, distinguishable by age of onset, allergy status, airway inflammatory pattern and response to treatment.[4] Eosinophilic asthma is the most commonly studied inflammatory phenotype, driven by T2 cytokines and present in approximately 50% of asthmatics, with both allergic and nonallergic triggers initiating or aggravating the disease. In contrast, the relevance and driving factors in non-T2 asthma, including neutrophilic asthma, are less well-defined and often precipitated by various factors including pathogens, air pollutants, cigarette smoke, cold air or exercise.[5] Finally, the pauci-granulocytic phenotype may reflect either well-treated airway inflammation or symptomatic severe asthma driven by episodic inflammatory or noninflammatory events, for example, airway smooth muscle (ASM) hypertrophy.[6] More recent data showed that different inflammatory signatures may be present at different anatomical sites within the airways of individual severe asthma patients.

Recent insights into molecular pathways underlying the inflammatory phenotypes helped to define distinct endotypes (Figure 1). Presently, the sub-endotype(s) of T2 asthma are best defined. T2-driven mechanisms are involved in epithelial barrier dysfunction, airway eosinophilia, mucus hypersecretion and airway hyperresponsiveness. In these patients, biologicals targeting T2-pathways, that is, IgE, IL-4, IL-5 and IL-13, showed an overall 50%-60% reduction in severe exacerbations.[7] Future studies will establish if biologicals to

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more upstream targets will safely deliver additional benefits, for example tezepelumab (anti-TSLP), which suppresses both IL-4/13, IL-5 pathways and also impacts non-T2 inflammatory events. However, targeted interventions so far did not achieve any disease-modifying effects and there is significant heterogeneity in treatment response due to the complexity of the T2 endotype. Additionally, recent health-economic evaluation showed that the cost of currently registered biologics for severe asthma exceeds the recommended maximal cost per quality-adjusted life-year by far.

Treatments targeting the following pathways: alarmins (eg TSLP, IL-25, IL-33), kinases (eg JAK, Pi3K) and other pro-inflammatory mediators (eg PGD2) are currently under clinical development while their long-term effectiveness remains to be seen. While bronchial thermoplasty may be considered for patients with severe asthma with predominant chronic airway obstruction due to ASM hyperplasia, non-T2 asthma and mixed endotypes still represent unmet needs.

Further understanding of the molecular pathways will help to elaborate accurate algorithms matching the right biological to the right patient. To this end, simple and reliable biomarkers are indispensable, which adequately reflect the underlying pathophysiology and the treatment response, as well as predict the long-term outcomes. In connection with the T2-signature, blood or sputum eosinophils and FeNO are presently the best validated biomarkers. While eosinophils can best be used to predict treatment response in eosinophilic (severe) asthma, FeNO proves useful in identifying T2 inflammation, partly unrelated to eosinophils and mainly IL-13-driven.

More innovative biomarker techniques, *that is* breathomics, require specific expertise including metabolomic analysis of exhaled air through mass spectrometry or eNose technology. Other emerging approaches include transcriptomics, genomics and micro-RNA analysis. Recent data showed that nasal epithelium gene profiling reflects bronchial gene expression and hence may serve as a future biomarker to guide asthma treatment. Alternatively, further

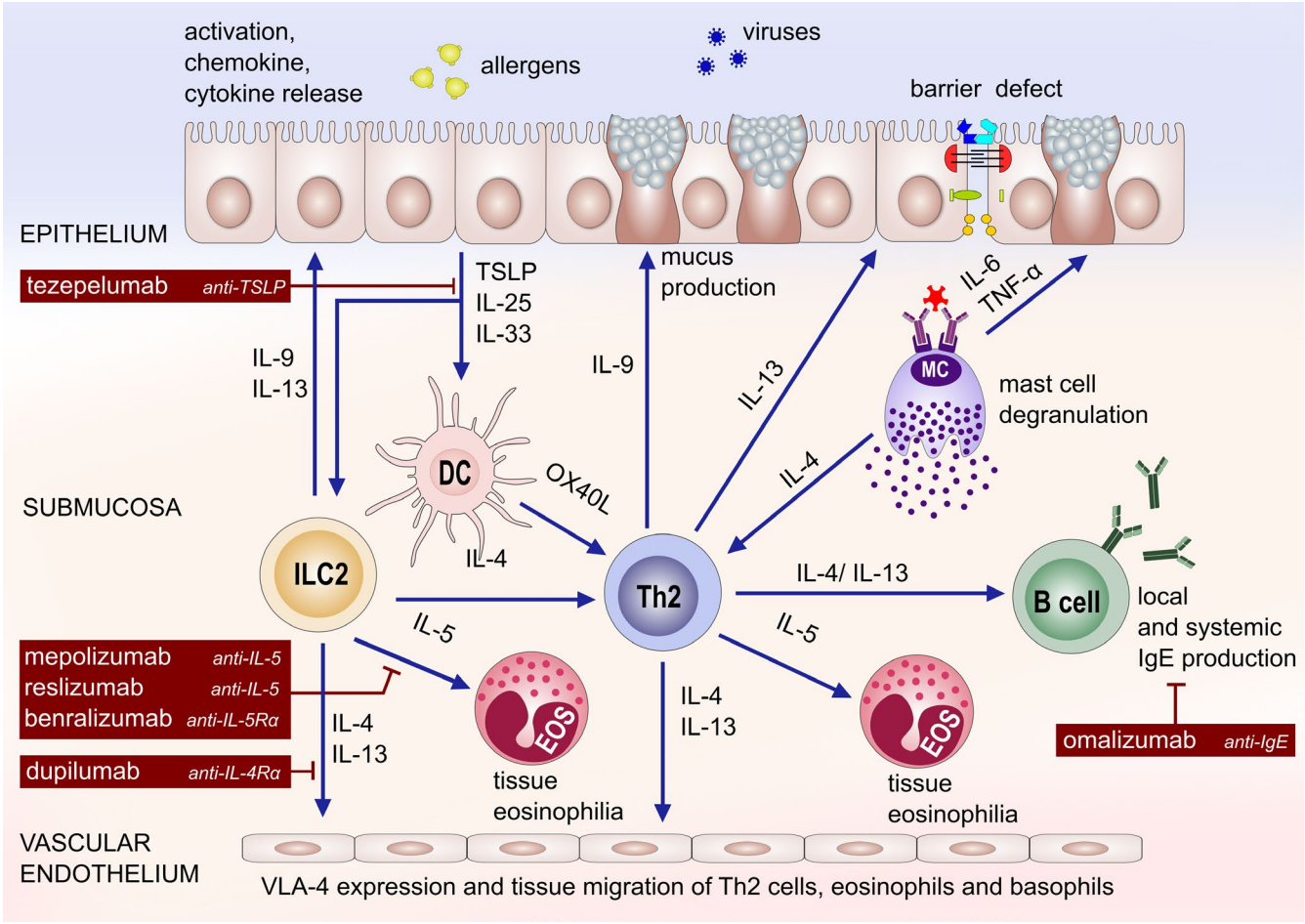


**FIGURE 1** Pathogenesis and targeted biological therapies of T2 asthma. Epithelial activation by allergens, viruses and pollutants leads to activation of epithelial cells and release of TSLP, IL-25 and IL-3, which lead to the activation of type 2 innate lymphoid cells (ILC) and dendritic cells. ILC2 play a role in T and B cell activation and recruitment and are early providers of Th2- and T-cell recruitment cytokines. A T2 type of an immune environment is characterized by IL-4, IL-5, IL-9, IL-13, IL-25, IL-33 production coming from Th2 cells, ILC2 and tissue cells. T2 environment is characterized by tissue eosinophilia, epithelial barrier defects, local IgE production, tissue migration of T2 related cells. Biologicals block several molecular aspects of these pathways such as omalizumab-IgE, dupilumab-IL4Rα, tezepelumab-TSLP, mepolizumab and reslizumab-IL-5 and benralizumab-IL5Rα. Eos, eosinophil; IL, interleukin; ILC2, innate lymphoid cell type 2; MC, mast cell; Th2, T helper 2 cell; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin; VLA-4, very late antigen-4

classifying biomarkers may arise from new imaging techniques and advanced physiology. Future pragmatic biomarker strategies, combining innovative methods for decoding the molecular, immunological, anatomical and physiological complexity, will further improve (sub) phenotyping, endotyping and personalized treatment.

Pulmonary rehabilitation is an alternative, effective but often overlooked treatment strategy.[8] However, patients should be informed on potentially detrimental effects of exposure to irritants such as chlorine by-products or cold air in specific training environments.

In childhood, the increased asthma risk after severe viral bronchiolitis may be due to long-lasting epithelial and innate immune changes, resulting in diminished antiviral immunity and enhanced pro-inflammatory T2 responses. Most children with T2 asthma respond well to low-dose ICS ± additional controller, but there are currently no predicting biomarkers for step-up to LABA, LTRA or increased ICS dose. Rather than increasing pharmacotherapy in the nonresponsive child, comorbidities, social and environmental factors should be addressed, especially poor adherence. In addition to omalizumab, at least 3 additional biologicals (mepolizumab, benralizumab, dupilumab) should become available soon for childhood severe asthma.[9] To enable personalized treatment approaches, further research into response predictors is key.

## CONFLICT OF INTEREST

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# The importance of social networks—An ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma

To the Editor,

The hygiene hypothesis was first proposed by Strachan in 1989, following his observation that hay fever was less common among children with older siblings.[1] Subsequent studies supported the association of family size, and more specifically birth order, with allergic sensitization. While initially focused on exposure to infectious agents and later microbes in general, the hygiene hypothesis is now considered by some to be a misleading misnomer and the focus on "hygiene" has