Asthma (M Jutel, Section Editor)

Endotype Driven Treatment of Asthma
Endotypes and Asthma Treatment

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Opinion Statement

The heterogeneity of asthma in relation to clinically significant outcomes, including response to treatment, has been established beyond any doubt. However, current treatment guidelines for asthma ignore disease heterogeneity and causal pathways. Extended heterogeneous disease-related metabolic, inflammatory, immunological, and remodeling pathways have been described, and a repetitive pattern is defined as a disease endotype. The response to targeted and non-targeted interventions in asthma may vary among individuals or for the same individual in relation to outcome measures (dissociated effect). Targeted treatment should be both biomarker-driven and outcome-driven. The ideal biomarker should be pathway-specific, reproducible, easily measurable, and affordable. Biomarker research in asthma is increasingly shifting from the assessment of the value of single biomarkers to multidimensional approaches, in which the clinical value of a combination of various markers is studied. Translation of biomarkers into pathway-specific diagnostic tests is essential and should guide the design of future large clinical trials, incorporating both longitudinal and mechanism-tailored endpoints. The selection of outcome measure is difficult, as it must reflect the mechanistic intervention and should be relevant for both the asthmatic population in general and the particular individual with asthma. While endotype-driven therapeutic strategies are increasingly successful, the issues of dissociated effect and drug efficacy at the target site remain unresolved. Efforts needed to move the field forward include profiling of Th2-low inflammation, incorporation of new targets, such as airway smooth muscle and epithelial components of asthma or epigenetics modifications, as well as application of systems pharmacology.

Introduction

It has recently become increasingly evident that antiasthmatic drugs are more effective in relation to certain molecular mechanisms of asthma, and hence the emergence of biomarkers to predict response to treatment.

Data have suggested that sputum eosinophils are accurate predictors for inhaled corticosteroids (ICS) response, both in corticosteroid-naïve patients and in cases of moderate/severe asthma, while neutrophilic inflammation was associated with lack of response. Other data sets have shown that the baseline values of clinical parameters, particularly lung function, are the major predictors of ICS response, and that blood or sputum eosinophils merely complement this data [1–5]. In addition, several reports have questioned the stability of the sputum eosinophilic phenotype over time, especially in the pediatric population [6, 7]. High levels of fractional exhaled NO (FeNO) have also been suggested as predictive of response to ICS, although the tailoring of treatment based on FeNO measurements did not decrease asthma exacerbations or increase asthma control [8]. There are several factors that influence FeNO levels, including age, atopy, medication use, and airway infections, and these must be considered when using FeNO for tailored interventions.

The accuracy of FeNO level surrogate for eosinophilic inflammation has been questioned in recent studies [9, 10]. One study that examined the use of blood eosinophils, FeNO, FEV1, and IgE levels, either alone or in combination, found that these were not accurate predictors of sputum eosinophilia [11]. A longitudinal study that assessed the relationship between sputum eosinophils and FeNO in children with asthma produced variable results in almost half of the subjects who produced more than one sputum sample, and it was not possible to identify a group in whom FeNO would consistently reflect eosinophilia [12]. The lack of correlation can be explained if we accept that FeNO and blood eosinophils reflect different endotypes of Th2-mediated inflammation. In a cross-sectional study, FeNO and blood eosinophil values offered independent information with respect to the prevalence of wheeze, asthma diagnosis, and asthma events [13•]. The authors suggest that blood eosinophilia is a marker of more severe systemic inflammation driven by a strong chemokine signal (such as IL-5) and more extensive eosinophilic airway inflammation involving the small airways, and therefore is ICS non-responsive. It may also highlight the risk of asthma exacerbations requiring oral corticosteroids. Further evidence was provided in the DREAM trial, which indicated that blood eosinophils were most closely related to a positive response to mepolizumab (anti–IL-5) [14••]. In contrast, an increased FeNO value indicated IL-4/IL-13–mediated Th2 inflammation localized in the bronchial mucosa responding to ICS or to IL-4/IL-13 blockade. Increased FENO value was a good predictor of a clinical response to lebrikizumab in the MILLY trial [15••].

Exhaled air metabolomics was recently evaluated as a predictor of ICS response. In patients with mild/moderate asthma, breath analysis by eNose predicted response with greater accuracy than sputum eosinophils or FeNO [16]. Studies are needed, however, to validate the clinical relevance of volatile organic compounds (VOCs), as well as longitudinal assessment of VOC patterns, in a large population of asthmatic patients.

A new concept: endotype-driven treatment of asthma

The hallmark characteristics of asthma, including inflammation, remodeling, and airway hyperreactivity, are governed by a complex network of molecules, sometimes repetitive across individuals with asthma. Although endotypes for asthma have been proposed, to date, no asthma endotypes have been definitively validated [17•, 18•]. The PRACTALL consensus report proposed several parameters for defining an asthma endotype: consistent clinical characteristics, biomarkers, lung physiology, genetic background, histopathology, epidemiology, and treatment response [19•]. The identification of corresponding molecular biomarkers for the individual pathogenic mechanisms underlying phenotypes or subgroups within a phenotype is essential (Fig. 1, Table 1). Longitudinal studies are necessary to validate whether newly defined asthma endotypes predict the individual course of the disease [18•].
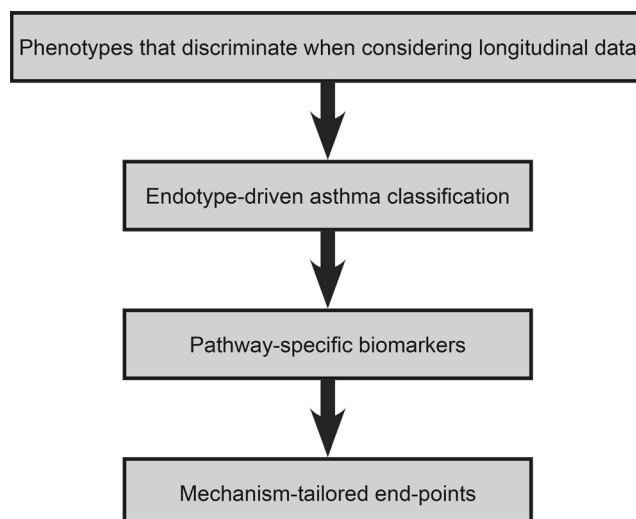
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Fig. 1. Essential steps to improve response to asthma treatment.

Unfortunately, asthma endotyping has focused primarily on Th2-high inflammation, which accounts for only half of the cases, while airway smooth muscle (ASM) and epithelial components and the Th2-low inflammation have been neglected [17•].

The Th2-high asthma endotype

In one study, the Th2-high molecular phenotype of asthma was described based on expression of periostin, human calcium-activated chloride channel 1 (CLCA1), and serpinB2, and characterized by increased expression of IL-5 and IL-13 in bronchial biopsies, airway hyperresponsiveness (AHR), serum IgE, blood and airway eosinophilia, subepithelial fibrosis, and airway mucin gene expression. The Th2 markers were reproducible on repeated evaluation. Response to ICS in the study was restricted to Th2-high asthma [20]. In a separate study, a qPCR-based assay of Th2 inflammation in bronchial biopsies was designed to overcome the limitations of the microarray-based method. The three-gene-mean of periostin, CLCA1, and serpinB2 correlated with FeNO, blood eosinophils, and PC20 methacholine, with greater improvement in FEV1 under ICS, and was a better predictor of improvement of lung function and symptoms than FeNO, blood eosinophils, IgE, or PC20 [21]. In induced sputum cell pellets, PCR was used to profile the gene expression of the epithelial cell signature of IL-13 activation and the Th2 genes as a noninvasive measure of Th2 inflammation. Gene expression levels of CLCA1 and periostin, but not SerpinB2, were significantly higher in sputum cells from asthmatics. Expression of IL-4, IL-5, and IL-13 was also significantly increased and highly correlated within individual subjects. By combining the expression levels of Th2 genes in a single quantitative metric (Th2

Table 1. Endotype-driven treatment of asthma

Endotype		Targeted intervention	Biomarker	Predictor of response	Measurable outcomes
Th2-high	IgE-driven (atopic and non-atopic)	Omalizumab, Quilizumab	Total serum IgE, Atopy, IgE on DC, Sputum total or specific IgE	Cumulated eosinophils/periostin/FeNO, Nasal polyps, Frequent exacerbations	Exacerbations, ?Airway obstruction and thickening (CT scan)
	IL-4/IL-13-driven	Lebrikizumab, Tralokinumab, Pitrakinra, Dupilumab	Periostin, Sputum IL-13 (tralokinumab) IL-4 rc α SNPs (pitrakinra)	EAR and LAR, Periostin, FeNO, Sputum IL-13 (tralokinumab), Blood/sputum eosinophils (dupilumab), IL-4 rc α SNPs (pitrakinra)	Lung function (depending upon asthma severity), Exacerbations, Treatment failure, Cough and sputum, Airway obstruction and thickening (CT scan)
	IL-5/eotaxin-driven	Mepolizumab, Reslizumab, Benralizumab	Sputum/blood eosinophils, FeNO, Eotaxin 2	Sputum/blood eosinophils, Frequent exacerbations, Nasal polyps, Late-onset asthma, Steroid-resistance, Uncontrolled asthma (ACQ)	Exacerbations, Lung function (reslizumab), AHR
	PGD2-driven	CRTH2 inhibitors	?	?sputum eosinophils	Lung function, Symptoms, QoL
	Aspirin-intolerant	Aspirin desensitization	Sputum/urine leukotrienes and prostaglandins	?	Aspirin-challenge, Exacerbations
	Mast cell/IL-9-driven	Anti IL-9 (MEDI-528)	?	EIB	QoL
	Eosinophilic obese asthma	?Antieosinophilic treatment	Sputum IL-5, Submucosal eosinophils	Sputum IL-5	Exacerbations, Symptom score
	Asthmatic granulomatosis (Th1-driven)	Immunosuppressants	Eosinophilic inflammation, Corticosteroid resistance, ?Autoimmunity markers	?	Lung function, Symptoms, OCS use
	Innate IR-driven	Anti TSLP	TSLP	?	?

Table 1. (Continued)

Endotype	Targeted intervention	Biomarker	Predictor of response	Measurable outcomes
Th2-low				
Neutrophilic (Th17/IL-8/purinergic inflammation-driven)	Anti 0x 40-0x 40 L CXCR2 antagonists Brodalumab	IL-33/ST-2 Sputum neutrophilia Low IgE Low eosinophils High reversibility (brodalumab)	Sputum neutrophilia High reversibility (brodalumab)	Exacerbations, lung function
Paucigranulocytic (EMTU-driven)	Phenotype switch of ASM into a quiescent cell (miRNA) Reduce ASM mass (bronchial thermoplasty) Correct epithelial dysfunction Increase antiviral properties (IFN β)	No inflammation (sputum/ bronchial biopsies) Prominent remodeling Severe viral-induced asthma exacerbations ?IP-10	Severe asthma Prominent AHR Lung function fluctuation Severe viral-induced asthma exacerbations	QoL Exacerbations Symptoms Lung function Airway obstruction and thickening (CT scan) Epithelial structure
Small airways disease	Ultrafine particles, systemic treatment	Flow, resistance, ventilation, heterogeneity, Alveolar inflammation	Air trapping Lung attenuation	Asthma control Exacerbations Nocturnal symptoms AHR EIB LAR
Microbiome	Newer macrolides	Non-eosinophilic asthma	Exacerbation-prone Low eosinophils Older age Longer asthma duration PCR evidence of bacterial infections	Exacerbations LTRI Lung function QoL
Innate IR-driven	Anti TNF-α	BAL/sputum TNF-α	?	Exacerbations Lung function
Non-eosinophilic obese asthma	?Metabolic intervention	L-Arg/ADMA	?	Exacerbations Symptoms

Abbreviations:
ADMA = asymmetric dimethyl arginine; AHR = airway hyperreactivity; ASM = airway smooth muscle; BAL = broncho-alveolar lavage; EAR = early allergic reaction; EIB = exercise-induced bronchoconstriction; EMTU = epithelium-mesenchyme trophic unit; FeNO = fractional exhaled nitric oxide; IFN = interferon; IP10 = IFN-γ-inducible protein; LAR = late allergic reaction; L-Arg = L-arginine; LTRI = low respiratory tract infections; miRNA = micro RNA; PCR = polymerase chain reaction; QoL = quality of life; SNPs = single-nucleotide polymorphisms

gene mean), 70 % had Th2-high asthma, which was characterized by increased asthma severity and blood and sputum eosinophilia [22].

Several subtypes of the Th2-high endotype can be described based on the main operating molecular mechanism (Table 1).

IgE-driven Th2- high endotype

Omalizumab, an anti-IgE monoclonal antibody, has been found to have significant benefits for patients with moderate-to-severe uncontrolled allergic asthma, although predictors of response are limited. In the Inner City Asthma Study (ICAS), both sensitivity and exposure were better predictors of response [23]. A post hoc analysis of the EXTRA study confirmed the potential of Th2 biomarkers (FeNO, blood eosinophils, and serum periostin) as baseline predictors for the therapeutic benefit of omalizumab [24•].

IgE has been linked to asthma irrespective of atopic status. In patients with refractory non-atopic asthma, omalizumab resulted in a statistically significant reduction in FcεRI expression on basophils and plasmacytoid dendritic cells (pDC2). The omalizumab group showed an overall increase in FEV1 compared with baseline as well as a trend toward improvement in global evaluation of treatment effectiveness and asthma exacerbation rate [25•]. It is proposed that the mechanism is either targeting local IgE or balancing the innate immune response to multiple triggers of an exacerbation by decreasing FcεRI expression on pDC [26]. In the Inner City Asthma Study, omalizumab nearly eliminated seasonal peaks (both spring and fall) in exacerbations, with or without viral infection, by targeting the cell (pDC) at the crossroads of asthma exacerbation triggers [23].

Sputum samples from patients with intrinsic asthma showed increased levels of both total IgE and Der p-specific IgE, which may represent a specific biomarker for selecting patients with intrinsic asthma for anti-IgE-targeted intervention [27]. In a randomized double-blind placebo-controlled study of allergic and non-allergic patients with nasal polyps and comorbid asthma, omalizumab had a beneficial effect on airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and quality-of-life scores, irrespective of the presence of allergy [28]. The association with nasal polyps may also pinpoint responders to omalizumab in non-atopic asthma.

IL-4/IL-13-driven Th2-high endotype

The study of Lebrikizumab in Adult Patients With Asthma Who Are Inadequately Controlled on Inhaled Corticosteroids (MILR1444A – MILLY trial) was one the first monoclonal antibody trials in asthma to validate a biomarker consistent with the therapeutic intervention. In this double-blind placebo-controlled 6-month trial in patients with inadequately controlled asthma, the IL-13 blocking antibody lebrikizumab significantly improved FEV1 at 12 weeks [15••]. A decrease in the rate of severe exacerbations at the 32-week follow-up period was also reported [29]. Patient subgroups were prespecified according to baseline total IgE level, blood eosinophil count, and serum periostin. The level of periostin was associated with a better response in terms of FEV1 improvement. In a post hoc analysis, high baseline FeNO was also associated with greater efficacy of lebrikizumab in improving

lung function and decreasing severe exacerbations, although intrapatient variability was higher in baseline FeNO than in periostin levels during the run-in period. Adverse effects were similar to placebo, with the exception that musculoskeletal side effects occurred slightly more often with lebrikizumab. A dose-ranging study of lebrikizumab in adult patients not taking ICS (MOLLY trial) demonstrated no effect on FEV1 in this category of patients, including the periostin subgroup. However, lebrikizumab treatment was associated with a reduced risk of treatment failure at all doses, and results were similar in the periostin subgroup [30]. In a separate mild asthma trial, the late asthmatic response was reduced by 48 % in lebrikizumab subjects, although this was not statistically significant. Exploratory analysis indicated a greater reduction in late asthmatic response in subjects with elevated baseline levels of peripheral blood eosinophils, serum IgE, or periostin [31].

Further studies are needed to explore the relationship between FeNO and periostin. In the MILLY trial, both were separate predictors of response. In the BOBCAT trial, serum periostin was strongly correlated with persistent sputum and tissue eosinophilia despite steroid treatment; the correlation was present regardless of sputum or tissue neutrophil counts. FeNO measurement detected fewer subjects with tissue eosinophilia and exhibited greater overlap between eosinophil-low and eosinophil-high subjects. While sputum and blood eosinophil counts and FeNO levels are subject to significant temporal variability based upon allergen exposure, exacerbations, and steroid treatment, the BOBCAT trial showed relatively little intra-subject variability in serum periostin in 3 measurements over the course of up to 5 weeks. In a logistic regression model incorporating age, sex, body mass index (BMI), blood eosinophils, serum IgE, FeNO, and serum periostin levels, periostin was the most significant single predictor of composite airway eosinophil status [32•].

Tralokinumab (CAT-354) is a human IgG4 monoclonal antibody that potently and specifically neutralizes IL-13. In a phase IIa study enrolling 194 patients with moderate-to-severe uncontrolled asthma despite controller therapies, tralokinumab significantly improved lung function and decreased rescue medication use, but did not affect the Asthma Control Questionnaire (ACQ)-6 score (primary outcome) or asthma exacerbations. The incidence of treatment-emergent AEs was higher in the tralokinumab groups than in the placebo group. Neither atopy nor blood eosinophils were better predictors for response. However, there was a trend for better response in FEV1 and ACQ-6 score the in the sputum IL-13-positive subjects [33].

The IL-4 receptor α amino acid variations may be another predictor of response to anti–IL-4/IL-13 pathway inhibitors. Subjects homozygous for the rs8832 common G allele responded to pitrakinra administration with a decrease in exacerbations, nocturnal awakenings, and limitation of activities by asthma. Both rs8832 and rs1029489, in addition to several other intronic SNPs (rs3024585, rs3024622, and rs4787956), demonstrated a significant pitrakinra dose–response association with reduced asthma exacerbations. These SNPs were not associated with asthma exacerbations in the placebo group. The predictive power of SNPs, however, was present only in the low-eosinophil-count group [34].

The efficacy and safety of dupilumab, a fully human monoclonal antibody to the α-subunit of the interleukin-4 receptor, was evaluated in pa-

tients with uncontrolled persistent moderate-to-severe asthma who were preselected based on elevated blood or sputum eosinophil levels. The study evaluated the effects of dupilumab when added to background therapy, after long-acting acting beta-2 agonists (LABA) discontinuation, during the tapering of ICS, and as monotherapy. Dupilumab was associated with fewer asthma exacerbations when LABAs and ICS were withdrawn and with improved lung function and reduced levels of Th2-associated inflammatory markers (FeNO, IgE, plasma eotaxin-3) [35•].

IL-5 driven Th2-high endotype

Mepolizumab, a humanized monoclonal antibody against IL-5, reduced the risk of asthma exacerbations in two small proof-of-concept studies. Patients with severe corticosteroid-resistant asthma were selected based on sputum eosinophilia and history of severe asthma exacerbations [36, 37]. The Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial tested the efficacy of mepolizumab for reducing the frequency of asthma exacerbations in severely asthmatic adults. The 621 adult subjects were selected based on history of severe exacerbations and evidence of eosinophilic inflammation, defined as either increased sputum or blood eosinophils, FeNO of 50 ppb or more, or prompt deterioration of asthma control after a reduction of 25 % or less in regular maintenance inhaled or oral corticosteroids [14••]. All three doses of intravenous mepolizumab significantly reduced exacerbations, delayed time to first exacerbation, and decreased exacerbations requiring hospitalization or ER visit. Both sputum and blood eosinophils were significantly reduced, although there was no change in lung function or quality-of-life (QoL) measures. Efficacy of mepolizumab increased with increased baseline eosinophil count and number of exacerbations in the previous year. Baseline FeNO proved to be less predictive than blood eosinophil count of response to treatment. The overall frequency of serious adverse events was similar across treatment groups.

Different results were obtained with reslizumab, another humanized monoclonal antibody anti-IL-5. In 53 subjects with persistent sputum eosinophilia and poorly controlled with ICS, reslizumab improved ACQ score only in patients with baseline ACQ scores >2 and those with nasal polyps. All patients in the reslizumab group showed a significant improvement in lung function, and sputum and blood eosinophils were reduced significantly. There was no effect on asthma exacerbations, likely due to the short duration of the study (15 weeks). Adverse events were similar to placebo [38].

The Th2- low asthma endotype

Based on data from Th2-high/low molecular signature studies, the incidence of Th2-low asthma accounts for 30–50 % of adult asthma cases [20–22]. Moderate or low response to ICS is characteristic, and a broad spectrum of asthma severity is included. Similar to the Th2-high endotype, several distinct subendotypes can be described (Table 1).

Neutrophilic asthma

Historically, anti-neutrophil agents such as anti-IL-8 have not met with much success. An orally active small-molecule antagonist of CXCR2 (SCH-527123) was recently tested in patients with severe asthma and sputum total cell count $<10 \times 10(6)$ /g and neutrophils >40 %. SCH-527123 proved successful in reducing sputum neutrophil numbers, suggesting improvement in clinical outcomes such as mild exacerbations and ACQ scores. There was no effect on lung function or sputum neutrophil activation markers (myeloperoxidase, IL-8, or elastase). In terms of safety, the mean absolute neutrophil count in blood was reduced by 14 % at the end of 4 weeks, but recovered by the 5th week, and there were no differences in the overall rates of adverse events compared to placebo [39].

The efficacy and safety of brodalumab, a human anti–IL-17 receptor A monoclonal antibody, was recently evaluated in subjects with inadequately controlled moderate-to-severe asthma taking regular ICS. The primary end-point was change in ACQ, and secondary endpoints included FEV1, symptom scores, and symptom-free days. Although there was no evidence of treatment of brodalumab in the overall study population, a high bronchodilator reversibility criteria (>20 %) identified a potential subpopulation for clinically meaningful response. Other prespecified subgroups (baseline FEV1% predicted, ACQ, ICS dose, FeNO, peripheral eosinophils, sex, race and weight) did not predict response [40•]. Unfortunately, patients were not evaluated for their sputum inflammatory phenotype (eosinophilic or neutrophilic).

Paucigranulocytic asthma (EMTU-driven endotype)

A combination of studies on airway biopsies and primary cell cultures suggests that asthma is primarily an epithelial disease driven by increased environmental susceptibility to injury and an altered repair response as depicted by sustained activation of the epithelial mesenchymal trophic unit (EMTU) [41].

Significant advances in understanding the cell and molecular biology of inflammation and ASM contractility suggest an ASM asthmatic endotype and have identified several potential novel therapeutic targets [42]. Targeting G-protein-coupled receptors such as bitter taste receptors (TAS2R) may be an area of interest. In addition to the recently described bronchodilator and anti-inflammatory properties [43], their increased expression was shown in peripheral blood leucocytes of asthmatic children and in the airways of severe asthma patients [44, 45]. TAS2R agonists were effective in relaxing ASM even when β2-adrenergic receptors were subject to tachyphylaxis. In addition, IL-13 caused a decrease in β-agonist-mediated relaxation, while TAS2R-mediated relaxation was unaffected [46]. The cAMP/PKA pathway continues to be a promising drug target with the emergence of new phosphodiesterase-E inhibitors and a novel PKA target protein, HSP20, which mediates ASM relaxation via actin depolymerization. Inhibitors of the RhoA/Rho kinase pathway can also elicit ASM relaxation. Targeting epigenetic processes that control chromatin remodeling and RNA-induced gene silencing also holds great potential for "switching" of the ASM asthmatic endotype [42].

Ciliary dysfunction has been documented in moderate and severe asthma. The lack of correlation with eosinophilic inflammation indicates a distinct endotype associated with aberrant epithelial repair and infection [47]. Both short- and long-acting β2-agonists are reported to increase ciliary beat frequency [48]. Therapy directed at ciliary dysfunction may represent a new treatment approach for this asthma endotype.

Lung epithelial cells can influence immune responses to allergens, viruses, and other triggers, as well as subsequent inflammation and repair. Barrier epithelial cells sense exposure via pattern recognition receptors and activate innate immune cells through the secretion of thymic stromal lymphopoietin (TSLP), GM-CSF, IL-1, IL-33, and IL-25 [41]. Inhibiting the IL-33/ST-2 axis may reduce the epithelial potential to induce a local Th2 orientation. TSLP is a potential noninvasive biomarker released from activated epithelial cells [49]. Specific humanized antibody that blocks interaction between TSLP and TSLP receptor or OX40 and OX40 ligand are currently being developed [50].

Airway epithelial cells are important initiators of the local antiviral immune response through the production of chemokines, proinflammatory cytokines, and interferons (IFN). An in vitro study showed that budesonide and formoterol can inhibit cell inflammatory responses in HBECs without interfering with viral replication or production of interferons [51]. Defective rhinovirus (RV)-induced IFN-β and IFN-λ production and increased RV replication have been reported in primary human bronchial epithelial cells (HBECs) from subjects with asthma [52]. In vitro addition of IFN-β to HBEC restores the normal antiviral response [53]. Delivery of IFN-β to the lungs of asthmatics may limit the spread of the virus to the lungs and consequent exacerbation. The phase II trial of inhaled IFN-β (SNG 001) enrolled 134 adult asthmatics recruited during a cold episode. Patients taking IFN-β showed lower asthma symptoms, a 65 % reduction in exacerbations, and quicker lung function recovery. The response was significant only in patients with difficult-to-treat asthma [54].

Microbiome-driven Th2-low asthma phenotype

Several studies have reported the distortion in airway bacterial community structure and composition in asthma, with greater abundance of members of the Proteobacteria, particularly *Haemophilus* species, and lesser abundance of members of the Bacteroidetes, particularly *Prevotellaceae* [55, 56]. Disordered microbiome was related to greater AHR and corticosteroid resistance [57, 58•].

Two approaches that may be considered to restore the normal bronchial microbiota are low-dose long-term antibiotic treatment and bacteriotherapy using the model promoted for gut microbiota.

Long-term macrolide antibiotics may be helpful due to their ability to regulate the altered microbiome, due to their antineutrophilic potential (decreased IL-8 production, neutrophil migration and/or function), or due to antiviral actions and the ability to restore corticosteroid sensitivity [59].

Predicting response to macrolides is still difficult. In one trial, responders were older and had a longer duration of asthma [60]. Other studies have suggested that PCR identification of *Mycoplasma* and *Chlamydophila pneumoniae* or neutrophilic inflammation best identifies the macrolide responsive phenotype [61, 62]. In the AZISAST study, subjects with exacerbation-prone severe asthma received low-dose azithromycin or placebo as add-on treatment to combination therapy of ICS and LABA for 6 months. While there was no difference between groups in the rate of severe exacerbations and lower respiratory tract infections requiring treatment with antibiotics, there was a significant difference in the predefined subgroup of subjects with non-eosinophilic severe asthma. There were no significant effects on lung function. Azithromycin was well-tolerated but was associated with increased oropharyngeal carriage of macrolide-resistant streptococci [63•].

Obese asthma phenotype

Analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI suggests that obesity-associated severe asthma represents a distinct clinical phenotype with greater requirements for maintenance corticosteroid, steroid burst therapy, and reliever use per day. These patients have shown reduced FVC and elevated carbon monoxide transfer coefficient. Serum IgE levels decreased with increasing BMI, and the obese group was more likely to report eczema but less likely to have a history of nasal polyps [64].

Excess BMI is an established risk factor for asthma, particularly in women. While it has been hypothesized that the metabolic syndrome mediates the BMI–asthma association, the CARDIA study found that BMI was a stronger predictor than metabolic syndrome for incident asthma in women. These results suggest that the BMI–asthma association is attributable to biomechanical, metabolic, or inflammatory abnormalities associated with obesity that are not part of the metabolic syndrome [65•]. In a cross-sectional comparison between early- and late-onset asthma phenotypes in the Severe Asthma Research Program, subjects with late-onset asthma had a higher median plasma asymmetric dimethyl arginine (ADMA) level and lower median plasma L-arginine. The log of plasma L-arginine/ADMA was inversely correlated with BMI and was associated with less IgE, increased respiratory symptoms, lower lung volumes, and worse QoL. The authors suggest abnormal metabolic pathways in obese asthma featuring an ADMA-driven impairment in protective NO synthesis. This obese asthma endotype is particularly relevant for patients in whom inflammation is not predominant and who are less responsive to anti-inflammatory strategies [66•]. In 131 subjects with severe asthma categorized into lean, overweight, and obese groups defined by their BMI, sputum IL-5 geometric mean was elevated in the obese compared with overweight and lean subjects and was correlated with BMI. In the bronchoscopy group, the submucosal eosinophil number was correlated with BMI, and the median number of submucosal eosinophils was higher in obese versus lean subjects. As this was a single-center study, further studies

replicating these results are needed, but this may suggest a subset of obese asthmatics where specific antieosinophilic therapy is beneficial [67].

Compliance with Ethics Guidelines

Conflict of Interest
Ioana Octavia Agache declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •   Of importance
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