Received: 8 June 2021 | Accepted: 9 August 2021

DOI: 10.1111/all.15054

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW ARTICLE

Advances and highlights in asthma in 2021

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[Correction added on 06_October_2021, after first online publication. The affiliations of Marek Jutel have been corrected.].

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Abstract

Last year brought a significant advance in asthma management, unyielding to the pressure of the pandemics. Novel key findings in asthma pathogenesis focus on the resident cell compartment, epigenetics and the innate immune system. The precision immunology unbiased approach was supplemented with novel tools and greatly facilitated by the use of artificial intelligence. Several randomised clinical trials and good quality real-world evidence shed new light on asthma treatment and supported the revision of several asthma guidelines (GINA, Expert Panel Report 3, ERS/ATS guidelines on severe asthma) and the conception of new ones (EAACI Guidelines for the use of biologicals in severe asthma). Integrating asthma management within the broader context of Planetary Health has been put forward. In this review, recently published articles and clinical trials are summarised and discussed with the goal to provide clinicians and researchers with a concise update on asthma research from a translational perspective.

KEYWORDS
asthma, biomarkers, endotypes, exacerbations, guidelines

Abbreviations: ACE, angiotensin-converting enzyme; AHR, airway hyper-responsiveness; AM, alveolar macrophages; ASM, airway smooth muscle; B1R/B2R, B1/B2 receptors; BAL, bronchoalveolar lavage; BAT, basophil activation test; BEC, bronchial epithelial cells; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CXCL1, chemokine C-X-C motif ligand 1; DCs, dendritic cells; EET, eosinophils extracellular traps; eNose, electronic nose; ETSA, thunderstorm asthma; FEV, forced expiratory volume; HDC, histidine decarboxylase enzyme; ICS, inhaled corticosteroids; IFN, interferon; IL, interleukin; IL1RL1, interleukin 1 receptor-like 1; ILC, innate lymphoid cell; ILR, interleukin receptor; LTBP, latent TGF-beta binding proteins; LysoPS, lysophasphatidylserine; mAb, monoclonal antibody; MANAclust, Merged Affinity Network Association Clustering; MCDA, multi-criteria decision analysis; MCs, mast cells; mDCs, myeloid dendritic cells; miRNAs, MicroRNAs; MRI, magnetic resonance imaging; NET, neutrophils extracellular traps; NKT, natural killer T cells; Non-T2, non type-2 immune response; OCS, oral corticosteroids; ORMDL3, ORMDL sphingolipid biosynthesis regulator 3; PAG1, phosphoprotein associated with glycosphingolipid-enriched microdomains 1; PBMCs, peripheral blood mononuclear cells; PD2, prostaglandin D2 receptor 2; PexA, particles in exhaled air; PFTs, pulmonary function testing; PGD2, prostaglandin D2; PRR, pattern recognition receptor; RAGE, receptor for advanced glycation end products; RSV, Respiratory syncytial virus; RV, rhinovirus; S1P, sphingosine-1-phosphate; SAA, serum amyloid A; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEA, severe eosinophilic asthma; SLT, secondary lymphoid tissue; STC1, epithelium-derived stanniocalcin-1;; T, lymphocytes; T2, type-2 immune response; Th, T helper lymphocytes; TLR, toll-like receptor; TMPRSS2, transmembrane protease serine 2; TNF, tumour necrosis factor; TNFR, tumour necrosis factor receptor; TSLP, thymic stromal lymphopoietin; VC, vital capacity.

1 | INTRODUCTION

A better understanding of the role of the resident cell compartment in asthma pathogenesis, the development of novel tools for endotyping, large randomized clinical trials and real-world evidence all contributed to a significant advance in the management of asthma in the past year (Box 1).

2 | ASTHMA PATHOPHYSIOLOGICAL MECHANISMS

Defining disease endotypes based on key pathophysiological mechanisms has become a rational development in asthma, as the endotype-driven approach offers a way to better diagnose, monitor and stratify patients.[1,2] Based on the major immune-inflammatory pathway involved, type-2 high (T2), type-2 low (non-T2) and mixed endotypes are described for severe asthma, with several shared pathophysiological pathways such as genetic and epigenetic, metabolic, neurogenic and remodelling subtypes.[3–6]

2.1 | Innate immunity

Dysregulated innate immunity is a common finding in asthma.

Upon exposome stimulation (allergens, pollutants and viruses), bronchial epithelial cells (BEC) release interleukin (IL)-33, IL-25 and thymic stromal lymphopoietin (TSLP) which mediate in turn group 2 innate lymphoid cell (ILC2) activation, survival and release of type-2 (T2) cytokines—IL-4, IL-13, IL-5, amphiregulin and IL-9.[7,8] Activation of c-Myc, a transcription factor implicated in cell proliferation and differentiation, licences ILC2 for IL-5 and IL-13 release.[9] ILC2 are more sensitive to outdoor pollution-driven proliferation than other ILC types.[10] ILC2s are deemed as steroid resistant, however, other asthma treatments might decrease their pro-inflammatory capacity.[11] An *in vivo* model showed that tiotropium attenuated ILC2-dependent airway inflammation by suppressing IL-4 production from basophils.[12] Signalling through oestrogen receptor α on BEC also increases IL-33 release.[13] A reciprocal positive feedback loop between TSLP and IL-33 further amplifies the inflammation.[14] IL-33 activates fucosyltransferase 2 which induces the fucosylation of BEC, paramount for sustained ILC2 activation.[15] In addition, human BEC expresses functional IL-5 receptor, the stimulation of which contributes to the impairment of epithelial barrier integrity.[16] BECs express soluble interleukin 1 receptor-like 1 (ST2) and IL-33 stimulation increases intracellular calcium, alters gene expression, but has no effect upon wound repair. Tumour necrosis factor (TNF)-α reduces the expression of ST2. BECs release spontaneously soluble ST2, an effect downregulated by TNF-α and poly-I:C. A reduction of the release of soluble ST2 could potentially increase free IL-33 leading to amplification of the underlying airway inflammation.[17]

Besides BEC, airway smooth muscle (ASM) and mast cells (MC) synthetize IL-33, and the extent of IL-33 production by these cells correlates with AHR. Of note, ASM and MCs also express the IL-33 receptor ST2, which indicates an autocrine role for IL-33 in these cells. IL-33 directly promotes MCs activation and ASM 'wound repair' type response and indirectly promotes ASM contraction via upregulation of MC-derived IL-13.[18] Lung MCs express muscarinic M3 receptors and respond to methacholine by releasing serotonin, which likely acts on nerves to release acetylcholine, thereby enhancing airway hyper-responsiveness (AHR). Tiotropium, which inhibits M3 preferentially, and reduces AHR in asthma patients, may act by targeting MC.[19] The increasing evidence of the anti-inflammatory effect of long-acting muscarinic antagonist (LAMA) in asthma might lead to changes in the positioning of these drugs in clinical guidelines.

Histamine is an important MC-derived immunomodulator influencing both the innate and adaptive immune response. Certain host cells express the histidine decarboxylase enzyme (HDC), catalysing the decarboxylation of histidine to histamine. Bacterial strains can also express HDC and secrete histamine. Histamine secretion from bacteria within the gut can have immunological consequences at distant mucosal sites, such as within the lung. These effects are influenced by host histamine receptor expression and the expression of histamine degrading enzymes.[20]

Danger signal recognition by the innate immune response plays an important role in modulating airway inflammation in asthma. Alveolar macrophages (AM) reside in the lung parenchyma, in direct contact with the environmental triggers. Following AM stimulation inducible nitric oxide synthase, Toll-like receptor (TLR), p38 mitogen-activated protein kinase, IL-1, IL-8, IL-17 and IL-10 signalling and chemokine C-X-C motif ligand 1 (CXCL1) are upregulated while genes associated with cell cycle and growth, DNA damage and

BOX 1 Major milestone discoveries

- New international guidelines both for mild and moderate/severe asthma advocate for a stratified approach in asthma management, focused on patient's needs and on the desired outcomes.
- Simplified dosing regimens for asthma controller medication are recommended as they improve adherence to long-term therapies.
- Real-world evidence has increased in quality and offers a solid support in formulating recommendations for care pathways and facilitating their implementation.
- The central role of the bronchial epithelium in the initiation and further modulation of the immune-inflammatory events in asthma is currently supported both by basic and translational research and by the efficacy of the biologicals targeting epithelial cytokines.
- The knowledge on the subendotypes of non-T2 asthma and on shared pathophysiological mechanisms has been expanded with the inclusion of epigenetic, metabolic and innate immune biomarkers.
- Novel tools like imaging, omics and AI models further support a precision medicine approach in asthma.

repair, insulin receptor and leptin signalling are downregulated.[21] Macrophage activation is attenuated in severe asthma patients as compared to healthy subjects.[22] Moreover, invariant natural killer T cells (NKT), T lymphocytes γδ and mucosal-associated invariant T cells synthetize more inflammatory cytokines in asthmatics than in healthy individuals.[23]

Activated eosinophils release extracellular traps (EET) which contribute to mucus viscosity and airway inflammation. Besides IL-5, the TLR2 agonist lysophosphatidylserine (LysoPS) triggers eosinophil degranulation and EET release, and eosinophils from severe asthmatics are more sensitive to LysoPS-mediated degranulation.[23] Moreover, EET induced the release of TLSP and IL-33 by BEC, and the accumulation of ILC2.[24] Neutrophils also release DNA extracellular traps (NET) and both EET and NET were associated with severity.[25] Eosinophils also express prostaglandin D2 (PGD2) receptor 2 (PD2). PD2 signalling mediates eosinophil activation and migration, release of IL-4, IL-5 and IL-13 by ILC2 and Th2 cells, and increase in smooth muscle mass.[26] Glucagon-like peptide-1 receptor agonist inhibited early innate airway inflammation in a mouse model in the setting of obesity, while TSLP or ST2 inhibition decreased airway eosinophils, but did not reduce airway neutrophils.[27] This observation deserves further evaluation as a potential therapeutic approach for obese asthma patients.

2.2 | T2 asthma

Contemporary hypotheses suggest that tissue perturbations, rather than direct antigen recognition, may be the primary driver of T2 immunity (Figure 1). Epithelial-derived cytokines and ILC2s initiate T2 asthma by driving dendritic cell (DC) activation and phenotypic changes in the airways, followed by their migration to secondary lymphoid tissues (SLT) where they present the allergen to naïve T cells and orient them towards a T2 profile (Figure 1). Myeloid DCs (mDCs), plasmacytoid DCs (pDCs) and monocyte-derived DCs are key players in the immune response in asthma. TSLP enhances CCR7 expression on mucosal CD1c+ mDC, thus enabling them to migrate to SLT.[28] IL-33 particularly programs CD1c+ mDCs to drive T helper lymphocytes (Th) 2 differentiation from naïve CD4+ T cells in SLT.[29] Serum amyloid A (SAA), a soluble pattern recognition receptor (PRR), acting on formyl peptide receptor 2 is a potent inducer of IL-33. SAA de-polymerization contributes to the T2-polarizing potential of CD1c+ mDC, thus suggesting that the conformational change or modification of sentinel proteins initiates the allergic cascade.[30] Other mediators also contribute to the maturation of mucosal CD1c+ mDCs. Colony-stimulating factor 1 licences CD1c+ mDCs to traffic to SLT after allergen uptake.[31] MicroRNAs (miRNAs) transferred between cells in extracellular vesicles regulate signalling pathways during inflammation. Secretion of miR-34a, miR-92b and miR-210 by BEC contributes to CD1c+ mDC maturation during the sensitization phase.[32] CD141+ mDC are specialized in antigen cross-presentation and are crucial for antiviral defence.[33] An activated status in epithelial CD141+ mDCs increases interferon (IFN)-γ availability, thus protecting from Th2-cell priming.[34] Moreover, plasmacytoid DCs are relevant sources of type I IFN and also protect from viral respiratory infections.[35] Importantly, the binding of the allergen to IgE/FcεRI complexes on cell surface abrogates type I IFN release by pDC, which might explain the increased susceptibility to viral exacerbations in allergic asthma patients.[36] On the other hand, monocyte-derived DC are the master local orchestrators of the effector phase of allergic asthma, as they excel in releasing chemokines (CCL13, CCL17, CCL18 and CCL24), recruiting T cells and eosinophils to the airways and in locally reactivating memory Th2 cells. Exosomes released by BECs stimulated with house dust mite allergen-containing contactin-1 facilitate the recruitment, proliferation, migration and activation of monocyte-derived DCs in cell culture and in mice.[37]

The source of IL-4 during Th2 priming in SLT is a matter of debate. Progranulin, a glycoprotein released by BEC, interstitial macrophages and fibroblasts triggers IL-4 secretion by NKT cells.[38] Besides IL-4, other factors regulate Th2 polarization in SLT. Phosphoprotein associated with glycosphingolipid-enriched microdomains 1 (PAG1) is a transmembrane protein regulating receptor signalling in T and B cells. Genetic variants in PAG1 were associated with asthma risk. PAG1 deficiency increased Th2 differentiation and favoured allergic sensitization.[39] Acid sphingomyelinase, a key regulator of sphingosine-1-phosphate pathway, promotes Th1 immunity in the airways. Mice deficient in acid sphingomyelinase have high numbers of Th2 cells in the bronchoalveolar lavage (BAL), but reduced IL-4 and IL-13 that ultimately translated into protection from T2 inflammation.[40] Protein S is a glycoprotein with anticoagulant, anti-inflammatory and anti-apoptotic properties. Protein S induces the release of IL-12 and TNF-α by bronchial mDCs, thus preventing Th2 polarization and decreasing AHR.[41]

IL-13 is a truly pleiotropic cytokine for its heterogeneity of cellular source and downstream functions.[42] A new subendotype of severe T2 asthma was recently reported, characterized by an increase in IL-13 BAL levels associated with increased neutrophils without eosinophils, in association with pathogenic bacteria: *Moraxella catarrhalis*, *Haemophilus sp.* and *Streptococcus sp.* This population may benefit from an IL-4/IL-13-targeted therapy, although the 'classic' T2 selection biomarker—blood or sputum eosinophilia is not immediately noticeable.[43] Therefore, these data might translate into a change in the selection criteria for biologicals in future.

2.3 | Non-T2 asthma

Non-T2 asthma, simplistically referred to as non-eosinophilic asthma, encompasses both inflammatory endotypes where non-T2 cytokines are involved in driving asthma pathobiology, as well as noninflammatory endotypes, which include structural abnormalities involving ASM as well as neuro-inflammation (Figure 1). Non-T2 asthma subendotypes can further be classified according to the nature of underlying airway inflammation, as characterized by sputum cytometry, and AHR. Key cytokines involved in non-T2 neutrophilic asthma are IL-17, IL-8 and IL-6. Paucigranulocytic asthma

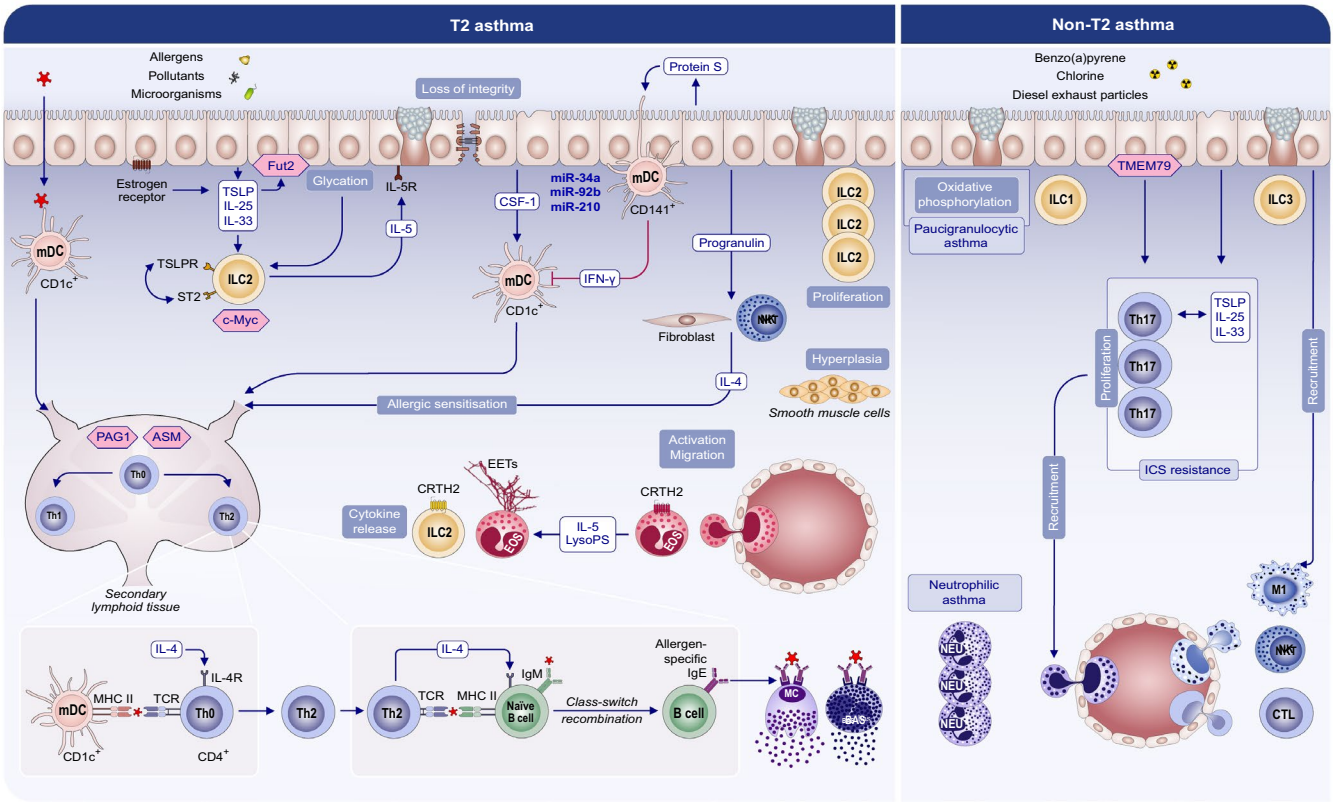

FIGURE 1 **T2 asthma:** Upon stimulation by allergens, pollutants or microorganisms, bronchial epithelial cells (BEC) release IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which in turn activate group 2 innate lymphoid cells (ILC2) in the bronchial mucosa. Signalling through oestrogen receptor on BEC also triggers IL-33 release. IL-33 induces the expression of fucosyltransferase 2 (Fut2) and the glycation of BEC. This effect contributes to sustained ILC2 activation in T2 asthma. A reciprocal positive feedback loop exists between TSLP receptor (TSLPR) and IL-33 receptor (ST2) expression on ILC2. The expression of c-Myc licences ILC2 to release IL-5 and IL-13. IL-5 stimulates BEC and contributes to the loss of epithelial integrity. Colony-stimulating factor 1 (CSF-1) and the micro RNAs miR-34a, miR-92b and miR-210 are epithelial-derived factors that licence CD1c+ myeloid dendritic cells (mDC) to traffic to secondary lymphoid tissues (SLT) during the sensitization phase of allergic asthma. On the other hand, BEC release protein S which in turn activates CD141+ mDCs. IFNγ derived from CD141+ mDC abrogates CD1c+ mDC migration to SLT. BEC also release progranulin which in turn activates fibroblast and natural killer T (NKT) cells to produce IL-4. This cytokine is mandatory for Th2 polarization of naïve T cells (Th0) in SLT. Allergen-loaded CD1c+ mDC migrates to the SLT where they stimulate Th0 naïve cells to acquire a Th2 phenotype upon the influx of IL-4. Subsequently, Th2 cells communicate with naïve IgM+ B cells to mediate their class switch recombination to IgE. Switched B cells release allergen-specific IgE which sensitizes resident mast cells and recruited basophils for activation in the airway mucosa. The expression of phosphoprotein associated with glycosphingolipid-enriched microdomains 1 (PAG1) and acid sphingomyelinase (ASM) also regulates Th0 polarization (Th1 vs Th2) in SLT. Besides IL-5, lysophosphatidylserine (lysoPS) triggers eosinophil degranulation and extracellular trap (EET) release in T2 asthma. ILC2 and eosinophils express CRTh2 (prostaglandin D2 receptor) the stimulation of which mediates cytokine release and cell proliferation and migration. Increased susceptibility to ILC2 proliferation and hyperplasia of smooth muscle cells are also observed in T2 asthma.
Non-T2 asthma: Paucigranulocytic asthma is characterized by the oxidative phosphorylation of BEC, whereas neutrophilic asthma is associated with the increased activation of group 1 and group 3 innate lymphoid cells (ILC1 and ILC3, respectively). Mutations in transmembrane protein 79 (TMEM79) drives the proliferation of Th17 cells which mediates in turn neutrophil recruitment. Several pollutants like benzo(a)pyrene, chlorine and diesel exhaust particles damage BEC and trigger TSLP, IL-25 and IL-33 release. These cytokines act synergistically with Th17 cells to drive inhaled corticosteroid resistance in neutrophilic asthma. Pollutants also contribute to M1 macrophage, NKT cell and cytotoxic T cell (CTL) recruitment to the airways

encompasses patients with absence of airway inflammation (eosinophilia and neutrophilia) with persistent symptoms and evidence of AHR. Underlying mechanisms for this endotype may be due to changes in ASM or airway inflammation not reflected in the lumen or detected by sputum cytometry.[44]

The heterogeneity of non-T2 asthma endotype was confirmed in a recent sputum transcriptomic analysis. Paucigranulocytic asthma was associated with oxidative phosphorylation in BEC, whereas neutrophilic asthma was characterized by group 1 ILC activation.[45] Local stimulation of Th17 cells often precedes neutrophilic infiltration of the airways. Mutations in the gene for transmembrane protein 79, a regulator of epithelial integrity, drives Th17 proliferation.[46]

Chronic exposure to benzo(a)pyrene was associated with neutrophil, NKT and CD8+ T cell recruitment to the airways.[47] Moreover, chlorine inhalation contributes to M1 macrophage recruitment and group 3 ILC stimulation.[48] Diesel exhaust particles act synergistically

with epithelium-derived cytokines to drive steroid resistance through the induction of Th17 cells.[49]

A novel preclinical model assessing new therapeutic strategies for the Th17/neutrophilic asthma endotype focused on the transcription factor aryl hydrocarbon receptor pathway was recently described.[50]

Baseline sputum tumour necrosis factor receptor (TNFR)1 and TNFR2 were significantly increased in neutrophilic vs non-neutrophilic asthma phenotypes, while serum markers did not differ. Azithromycin treatment significantly reduced sputum TNFR2 and TNF relative to placebo, specifically in non-eosinophilic participants.[51] These data reinforce the role of macrolides in the treatment of non-T2 asthma.

2.4 | Shared mechanisms

Severe airway epithelial barrier damage plays a significant role in the pathophysiology of asthma (Figure 2). The physical barrier function of the airway epithelium is tightly interwoven with its immunomodulatory actions, while abnormal epithelial repair responses may contribute to remodelling of the airway wall.[52–54] Several groups are exploring barrier restoration interventions. WIN55212-2, a non-selective synthetic cannabinoid belonging to the aminoalkylindole group with anti-inflammatory properties helps restore the epithelial barrier following rhinovirus infection.[55] Of note, the epithelium-derived stanniocalcin-1 (STC1) may be a novel candidate for an epithelium-derived relaxing factor. Serum STC1 was shown to be decreased in asthma and correlated with asthma control, lung function (FEV_1) and serum IL-13 levels. Intranasal administration of recombinant human STC1 blocked store-operated Ca^{2+} entry and further inhibited ASM cell contractility by suppressing Ca^{2+} -dependent myosin light chain phosphorylation. IL-13 suppressed STC1 release from BECs, whereas rhSTC1.[56]

Genes regulating sphingosine-1-phosphate (S1P) metabolism are both related to asthma susceptibility and expressed by BEC.[54] For example, ORMDL sphingolipid biosynthesis regulator 3 (*ORMDL3*) modulates ASM physiology, AHR and expression of chemokines and adhesion molecules.[57] BEC also express the receptor for advanced glycation end products (RAGE) and signalling through this receptor

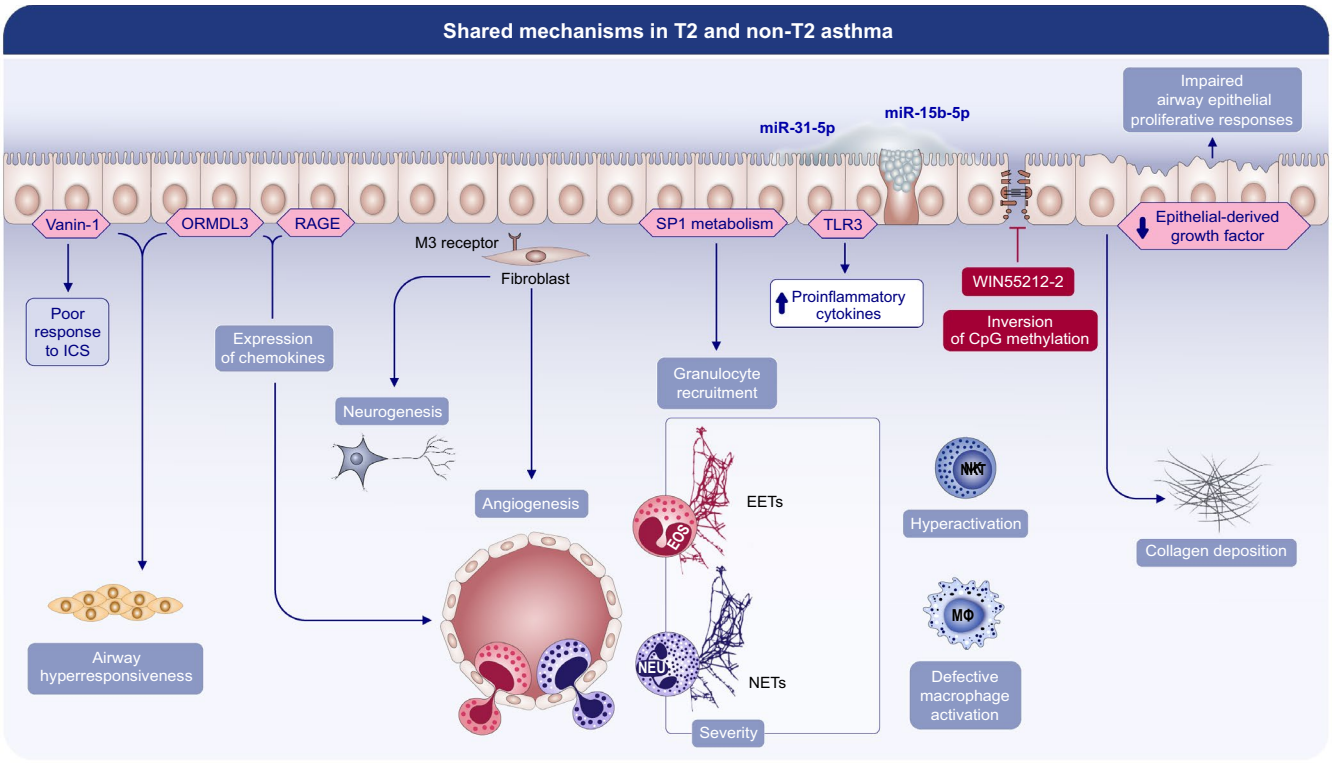

FIGURE 2 Shared mechanisms in asthma pathogenesis: Low expression of vanin-1 on bronchial epithelial cells (BEC) accounts for a poor response to inhaled corticosteroid in asthma. Vanin-1, together with ORMDL3, also modulates airway hyper-responsiveness. On the other hand, the expression of ORMDL3 and the receptor for advanced glycation end products (RAGE) on BEC favours inflammation and chemokine release. Signalling through TLR3 on BEC contributes to the production of inflammatory cytokines. Moreover, the expression of genes related to sphingosine-1-phosphate (S1P) metabolism on BEC drives granulocyte recruitment in asthma. Both neutrophils and eosinophils release extracellular traps (NET and EET, respectively) which are associated with asthma severity. Dysregulation of innate immunity is a common finding on asthma, including both the impaired activation of macrophages and the hyper-activation of NKT cells. On the other hand, signalling through M3 receptor on fibroblasts drives neurogenesis and angiogenesis. Some micro-ARNs, like miR-31-5p, contribute to mucus secretion by goblet cells. A decreased expression of epithelial-derived growth factor by BEC has been associated with defective proliferative responses and impaired healing capacity of the bronchial epithelium. Two novel interventions, WIN55212-2 and inversion of CpG methylation, have shown promising results for restoring epithelial integrity

promotes airway inflammation.[58] Bradykinin, acting on B2 and B1 receptors (B2R/B1R), enhances bronchial inflammation and induces fibroblasts to differentiate into α-smooth muscle actin myofibroblasts and to release proangiogenic factors. Moreover, signalling through muscarinic receptor M3 in fibroblasts contributes to angiogenesis and neurogenesis in severe asthma.[59] Importantly, the higher expression of B1R/B2R and B1R in severe asthma has been related to the extent of airway remodelling and fixed airway obstruction.[60]

Epigenetic modifications in BEC are associated with disease onset and therapy response in asthma. CpG methylation of specific genes contributes to epithelial barrier defects. The inversion of CpG methylation diminishes epithelium leakiness and increases the expression of tight junctions' proteins.[61] Moreover, the methylation status of inflammatory genes differentiates asthma patients from non-asthmatic subjects.[62] Decreased methylation and low expression of vanin-1 gene are associated with poor response to inhaled corticosteroids (ICS), whereas increased availability of cysteamine, a product of vanin-1 pathway, protects from AHR.[63] These findings suggest that epigenetic modulation represent a meaningful method to restore epithelial barrier integrity.

MicroRNAs (miRNAs) were recently involved in the association between viral infection and asthma development. In particular, miRNA-29s may be involved in the regulation of IL-33 through sST2 release. Elevated nasal, bronchial and/or exosomal levels of miRNA-29s in infancy may be useful biomarker for predicting later asthma development.[64] miRNA-31-5p regulates mucus secretion by goblet cells in both T2 and non-T2 phenotypes.[65]

Several mediators regulate both eosinophil and neutrophil recruitment to the airways. Semaphorin 3A is a neuron-derived protein with anti-inflammatory and anti-angiogenic activity, which blocks both neutrophilic and eosinophilic inflammation.[66] An imbalance in S1P metabolites or high levels of circulating miRNA-15b-5b drive both neutrophil and eosinophil recruitment.[67,68]

3 | PRECISION MEDICINE IN ASTHMA—BIOMARKERS AND NOVEL TOOLS

3.1 | Biomarkers

Biological markers (biomarkers) represent measurable indicators linking an endotype with a phenotype. Regrettably, current biomarkers are not precise in selecting the specific asthma endotype that will respond to a targeted treatment. A good example is the observation that blood eosinophilia predicts therapeutic response to all currently available interventions in severe asthma (ie anti-IL-5, anti-IL-4/IL-13 and anti-IgE).[69] Moreover, molecular markers of T2 airway inflammation do not differ between eosinophilic asthma and eosinophilic chronic obstructive pulmonary disease (COPD); however, the relationship between eosinophilia and T2 markers appears weaker in COPD than in severe asthma.[70] In addition, biomarkers are dynamic and temporally fluctuate, mirroring adaptive capacity to resist external perturbations. Longitudinal studies could cover this aspect, however, repeated sampling is very demanding, which limits its applicability. Presently, the most salient obstacles to ubiquitous biomarker usage are its feasibility and the cost of measuring samples. Work is under way to create rapid point-of-care tests that are both user-friendly and low-cost. The advent of these new methods combined with insights into biomarker combination strategies will likely yield robust information that will improve diagnosis and management of allergic diseases.

Exhaled breath volatile organic compounds signatures measured by electronic nose (eNose) have shown a promising potential for non-invasive asthma diagnosis and phenotyping where repeated sampling does not pose a major burden to patients. A recent small study showed that eNose profiles discriminated previral from postviral challenge phases in the asthmatic patients and healthy controls separately.[71]

The rate of activated basophils, in particular of those that express CD125, was inversely related to the effectiveness of anti-IL-5/IL-5Rα drugs, thus the basophil activation test (BAT) might prove an interesting tool for patient selection for a biological in severe eosinophilic asthma.[72] Upper airway immune mediator levels during episodes with asthma-like symptoms in young children were investigated in relation to their ability to predict response to azithromycin. Low levels of TNF-α and IL-10 and high levels of CCL22 predicted better treatment response.[73]

Significant differences in nasal epithelial DNA methylation were observed between non-severe and severe asthma in African American children, a subset of which may be useful to predict disease severity.[74] Sputum TNFR1 and TNFR2 were increased in severe asthma and correlated with poorer lung function, worse asthma control and increasing age. Serum TNFR1 was also increased in severe asthma. Sputum and serum TNFR2 were increased in frequent exacerbators.[45]

Advances have been made for biomarkers predicting future risk as well. Both short- and medium-term data suggest RV infection might serve as an important clinical marker of unstable preschool asthma. It has also been postulated that Vitamin D supplementation may have an anti-rhinovirus effect.[75] In a highly selected group of children with a history of early wheeze, ASM thickness and MC infiltration in infancy were associated with exercise-induced bronchoconstriction and wheezing episodes requiring hospitalizations by school age, while bronchial eosinophils in infancy were associated with increased AHR to methacholine at school age.[76] Early detection/prediction of flare-ups in asthma, commonly triggered by viruses, would enable timely treatment. eNose fluctuations rapidly increased after a rhinovirus-16 challenge, with distinct differences between healthy and asthmatic adults.[77] Genetic variants in interleukin 1 receptor-like 1 (*IL1RL1)* gene have been associated with susceptibility to asthma attacks in children.[78] Moreover, a defective upregulation of TLR2 and TLR4 in neutrophils was related to the delayed resolution of exacerbations triggered by infections.[79] Activated peripheral Th2 cells might represent a diagnostic biomarker for asthma exacerbations.[80] The characterization of allergen sensitization spectrum including the component-resolved

diagnosis in combination with clinical features may enable more accurate risk prediction for ryegrass pollen-related epidemic thunderstorm asthma (ETSA). It has been shown that Lol p 5 sensitization but not to Lol p 1 might be responsible for triggering ETSA[81]

Other biomarkers were related to asthma multimorbidity. Eight genes (CLC, EMR4P, IL-5RA, FRRS1, HRH4, SLC29A1, SIGLEC8 and IL1RL1) were consistently overexpressed in all types of multimorbidity for asthma, dermatitis and rhinitis. The multimorbidity signature was enriched in eosinophil-associated immune response and signal transduction. Protein-protein interaction network analysis identified IL-5/JAK/STAT and IL-33/ST2/IRAK/TRAF as key signalling pathways in multimorbid diseases.[82]

3.2 | Omics/AI models

Combining publicly available data from different omic sources could be a powerful approach to provide novel insights about the mechanisms of steroid responsiveness. Following this approach, a potential novel locus for ICS response in asthma patients was identified as latent TGF-beta binding proteins (LTBP)1, a member of the family of latent-transforming growth factor-beta binding proteins.[83]

Applying mass cytometry and machine learning to BAL cells from corticosteroid-resistant asthma generated two clusters: one enriched in IL-4+ innate immune cells and another dominated by IFN-γ+ T cells, including tissue-resident memory cells. The immune cell linkage developed through Exploratory Matrices (ICLite) algorithm showed signatures of mitosis and IL-7 signalling in CD206-FcεRI+CD127+IL-4+ innate cells in the first cluster, and adaptive immune responses in T cells in the other.[84]

Merged Affinity Network Association Clustering (MANAclust) is a coding-free, automated pipeline enabling integration of categorical and numeric data spanning clinical and multi-omic profiles for unsupervised clustering to identify disease subsets. MANAclust identified clinically and molecularly distinct clusters, including heterogeneous groups of 'healthy controls' and viral and allergy-driven subsets of asthmatic subjects. It also showed that subjects with similar clinical presentations have distinct molecular profiles.[85]

3.3 | Pulmonary imaging

Pulmonary functional imaging may be defined as the regional quantification of lung function by using primarily computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine techniques. The distribution of pulmonary physiologic parameters, including ventilation, perfusion, gas exchange and biomechanics, can be noninvasively mapped and measured throughout the lungs. This information is not accessible by using conventional pulmonary function tests, which measure total lung function without viewing the regional distribution. The latter is important because of the heterogeneous distribution of inflammation and remodelling in asthma. Significant strides have been made in this area for severe asthma (Table 1).

4 | RECENT MAJOR CLINICAL TRIALS IN ASTHMA

Simple dosing regimens improve adherence to long-term therapies (Table 2). As-needed budesonide/formoterol achieves better control and a lower exacerbation rate than as-needed terbutaline, while exposing mild asthmatics to less ICS than fixed-dose budesonide therapy.[86,87] This therapeutic approach excels in decreasing short-term exacerbations in adolescents with mild asthma,[88,89] a population at risk of severe asthma attacks. The PALLADIUM trial showed a comparable improvement in lung function between once-daily mometasone/indacaterol and twice-daily fluticasone/salmeterol.[90]

Prostaglandins and leukotrienes are the most studied eicosanoids and are established inducers of airway pathophysiology including bronchoconstriction and airway inflammation.[91] Fevipiprant is a selective PD2 antagonist blocking PGD2-mediated ILC2 and Th2-cell activation. Two clinical trials found no reduction in moderate-to-severe exacerbations in asthmatics ≥12 years receiving add-on oral fevipiprant, as compared to standard of care.[92]

LAMAs are recommended as add-on controllers in GINA step 5. Two trials investigated the effect of beclomethasone/formoterol/glycopyrronium in a single device (triple therapy) in adults with moderate-to-severe uncontrolled asthma[93] (Table 2). Patients on triple therapy achieved significantly better lung function than those on beclomethasone/formoterol. A post hoc analysis indicated that triple therapy decreased the rate of exacerbations especially in patients with higher reversibility at baseline.[94] The CAPTAIN trial also showed that fluticasone/umeclidinium/vilanterol improved lung function in adults with uncontrolled asthma, as compared to fluticasone/vilanterol.[95] Recently, tiotropium proved to be equally effective as ICS to treat mild asthma with low sputum eosinophilia.[96]

Tezepelumab, an anti-TSLP monoclonal antibody (mAb), reduced exacerbations and improved lung function, asthma control and quality of life in moderate-to-severe uncontrolled patients of different phenotypes.[97,98] Importantly, tezepelumab reduced exacerbations across all seasons,[99] and in patients with and without chronic rhinosinusitis.[100] Tezepelumab also decreased AHR (measured by mannitol) and airway inflammation (measured in bronchial biopsies) as compared to placebo.[101] Three additional trials are ongoing to assess the capacity of tezepelumab to reduce oral corticosteroids (OCS) intake[102] and airway inflammation,[103] and to investigate its long-term safety profile in severe asthmatics.[104] Astegolimab, a mAb targeting ST2 (IL-33 receptor), decreases exacerbations in adult patients with severe asthma regardless of blood eosinophils.[105] Overall, these findings outline the potential of mAbs blocking epithelial cytokines signalling to improve both T2 and non-T2 asthma outcomes (Table 2).

A post hoc analysis of QUEST assessed the efficacy of dupilumab in adolescent patients aged 12–17 years compared with adults aged ≥18 years. Dupilumab improved lung function and reduced levels of T2 biomarkers.[106] In another post hoc analysis, in a T2 asthma subgroup receiving high-dose ICS dupilumab significantly reduced severe exacerbations and improved lung function and asthma control.[107]

TABLE 1 Imaging methods for assessing pathological features occurring in severe asthma

Feature assessed	Imaging tool	Key findings	Reference
Bronchial thickening	MRI with Ultrashort Echo Time (UTE)	An accurate and reliable radiation-free method to assess bronchial wall dimensions, with enough spatial resolution to differentiate severe from non-severe asthma	135
Mucus plugs	Multidetector computed tomography (MDCT)	Quantifying airway mucus plugging suggest that treating mucus plugs may improve airflow in chronic severe asthma	136
	Mucus plugs contribution to ventilation heterogeneity (MRI VDP)	Mucus plugs were strongly associated with measures of airflow obstruction and with biomarkers of T2 and eosinophilic inflammation	137
Lung ventilation heterogeneity	Lung clearance index, free-breathing pulmonary ^{1}H magnetic resonance imaging (FDMRI) and inhaled-gas MRI to generate VDP	FDMRI VDP generated in free-breathing asthmatic patients was correlated with static inspiratory breath-hold ^{3}He MRI VDP but underestimated VDP relative to ^{3}He MRI VDP. Although less sensitive to salbutamol and post-methacholine challenge FDMRI VDP may be considered for asthma patient evaluations at centres without inhaled-gas MRI	138
	Ventilation/perfusion single-photon emission computed tomography (V-P SPECT)	V-P SPECT is promising as an objective measure to assess lung ventilation and perfusion to observe and assess responsiveness to mepolizumab. With quantification, this measure may allow better precision in determining treatment improvements.	139
	Hyperpolarized gas with helium (HHe-3) MRI	In children with asthma, greater ventilation heterogeneity index measured by HHe-3 MRI identified a T2 severe phenotype and mapped to regions of lung eosinophilia	140
	Hyperpolarized xenon-129 magnetic resonance imaging (129Xe-MRI)	129Xe-MRI is a sensitive marker of ventilation inhomogeneity in paediatric severe asthma and may potentially be used as a biomarker to assess disease progression and therapeutic response.	141
Accelerated longitudinal decline in lung function	Quantitative CT (qCT)	qCT measures of more severe airway remodelling, smaller airway disease and hyperinflation, and less pointwise regional change in lung volumes were associated with future lung function decline and asthma exacerbations	142

Abbreviations: CT, Computed tomography; MRI, magnetic resonance Imaging; VDP, ventilation defect per cent.

Adults with severe eosinophilic asthma (SEA) and chronic rhinosinusitis with nasal polyps, who experienced ≥2 prior-year exacerbations despite high-dosage ICS plus an additional controller had a clinically meaningful improvement in the Sino-Nasal Outcome Test-22 (SNOT-22) after treatment with benralizumab (ANDHI trial).[108]

5 | REAL-WORLD EVIDENCE AND PHARMACOECONOMIC CONSIDERATIONS

The introduction of biologicals and their expanding use over the last few years have transformed the management of severe asthma. Unfortunately, their very high cost also creates new challenges in terms of access and sustainability. Therefore, the real-world and health economics studies with biologicals are of great value to support the wider use of these therapies.

In a real-world study, the patients with non-atopic severe asthma achieved improved disease control after 1 year of treatment with omalizumab, similarly to asthmatics with allergic asthma. A marked reduction in unplanned visits and absenteeism from school or workplace was observed. 75.92% of the patients receiving OCS at entry stopped OCS treatment. A reduction of healthcare costs was also demonstrated.[109] A significant benefit was shown in a large case series examining the effects of benralizumab in subjects with severe eosinophilic asthma (SEA) with a suboptimal response to mepolizumab. A minority of patients had no clear benefit from switching to benralizumab.[110] In another analysis of a real-world cohort of patients with OCS-dependent SEA, a decrease in ICS use during the year of benralizumab treatment was shown. However, the suboptimal ICS adherence did not affect exacerbation frequency, ability to withdraw OCS or symptoms scores.[111]

TABLE 2 Recent Major Clinical Trials in Asthma

	Age (years)	N	Duration (weeks)	Baseline therapy	Investigative drug	Comparator	Primary outcomes	Secondary outcomes	Results
Anti-inflammatory therapy									
SYGMA 1 [94,96]	≥12	3849	52	GINA 1–2	B/F (as-needed)	T (as-needed)	Asthma control	Annualized rate of severe exacerbation	Asthma control was better and the rate of exacerbations was lower with as-needed B/F
SYGMA 2 [95]	≥12	4215	52	GINA 2	B/F (as-needed)	B (twice-daily)	Annualized rate of severe exacerbation	Asthma control ICS exposure	Comparable rate of exacerbations. Better control with twice-daily B and less ICS exposure with as-needed B/F
LUSTER 1 [100]	≥12	894	52	GINA 4–5	Fevipiprant (add-on)	Placebo	Annualized rate of moderate -to-severe exacerbation	Safety	Comparable rate of exacerbations and adverse events between fevipiprant and placebo
LUSTER 2 [100]		877							
Bronchodilators									
PALLADIUM [98]	12–75	2216	52	GINA 3–5	M/I (once-daily)	M (once-daily) FL/S (twice-daily)	Lung function at week 26	Safety	Lung function was better with M/I than M, and comparable between M/I and FL/S. The rate of adverse events was similar among the groups.
TRIMARAN [101]	18–75	1155	52	GINA 4 uncontrolled	BE/F/G (twice-daily)	BE/F (twice-daily)	Lung function at week 26. Annualized rate of moderate -to-severe exacerbation	Safety	Lung function was better and exacerbation rate was lower with BE/F/G. Adverse events were similar between groups.
TRIGGER [101]		1437		GINA 5 uncontrolled		BE/F (twice-daily) BE/F (twice-daily)+TI (once-daily)			Lung function was better with BE/F/G than BE/F, and comparable between BE/F/G and BE/F+TI. Exacerbation rate was comparable between BE/F/G and BE/F and between BE/F/G and BE/F+TI. Adverse events were similar among groups.
CAPTAIN [103]	≥18	5185	52	GINA 3–5	FL/V/U (once-daily)	FL/V (once-daily)	Lung function at week 24	Annualized rate of severe exacerbation	Lung function was better with FL/V/U and the rate of severe exacerbation was comparable between groups.

(Continues)

TABLE 2 (Continued)

	Age (years)	N	Duration (weeks)	Baseline therapy	Investigative drug	Comparator	Primary outcomes	Secondary outcomes	Results
Biologicals									
PATHWAY [105]	18–75	550	52	GINA 4–5	Tezepelumab (add-on)	Placebo	Annualized rate of severe exacerbation	Lung function Safety	Exacerbation rate was lower and lung function was better with tezepelumab. Adverse events were more common with the high dose of tezepelumab than placebo
NAVIGATOR [106]	18–80	1061	52	GINA 4–5	Tezepelumab (add-on)	Placebo	Annualized rate of exacerbation	Lung function Asthma control Quality of life	Exacerbation rate was lower and lung function, asthma control and quality of life was better with tezepelumab
SOURCE [110]	>18	NA	48	OCS-dependent asthma	Tezepelumab (add-on)	Placebo	OCS reduction	Exacerbation rate Lung function PROs	Ongoing
DESTINATION [112]	18–80 and 12–17	NA	Long-term (1 year) extension of NAVIGATOR and SOURCE	GINA 4–5	Tezepelumab (add-on)	Placebo	long-term safety and tolerability	Long-term effect of on asthma exacerbations Clinical effect after treatment cessation	Recruiting
UPSTREAM [109]	18–75	40	12	Uncontrolled	Tezepelumab (add-on)	Placebo	AHR Inflammation	Lung function Asthma control FeNO	AHR, airway inflammation and FeNO were lower with tezepelumab. No effect on lung function and control
ZENYATTA [113]	18–75	502	52	GINA 5	Astegolimab (add-on)	Placebo	Annualized rate of severe exacerbation	Time to the first exacerbation Asthma control Lung function Quality of life	Exacerbation rate was lower and time to the first exacerbation was longer with astegolimab. Control and lung function were comparable between astegolimab and placebo. Quality of life was better with the highest Astegolimab dose, and showed no difference with placebo for the other doses.

Abbreviations: B, budesonide; BE, beclomethasone; F, formoterol; FL, fluticasone; G, glycopyrronium; GINA, Global Initiative for Asthma; I, indacaterol; ICS, inhaled corticosteroids; M, mometasone; S, salmeterol; T, terbutaline; TI, tiotropium; U, umeclidinium; V, vilanterol.

Economic analyses can be extremely useful to guide decision-making and prioritization of care. Unfortunately, current analyses of cost-effectiveness conducted for the use of biologicals in asthma provide variable results. Multi-criteria decision analysis (MCDA) is an emerging approach where results of economic analyses are included in a comprehensive data matrix organized by criteria, along

TABLE 3 International asthma guidelines

Guideline	Highlights	Reference
GINA 2021	• Interim guidance about asthma and COVID-19 • Mild asthma: GINA does not distinguish between so-called 'intermittent' and 'mild persistent asthma' • Severe asthma definition has been clarified and is now worded without reference to GINA Steps. Severe asthma is asthma that is uncontrolled despite high-dose ICS-long-acting beta2 agonist (LABA), or that requires high-dose ICS-LABA to remain controlled • Description of populations in clinical trials and observational studies by the treatment they are prescribed rather than by a specific treatment 'Step'. Severity should not be imputed from current treatment • Treatment tracks for adults and adolescents: a. Track 1, with low dose ICS-formoterol as the reliever, is the preferred approach b. Track 2, with SABA as the reliever, as an alternative approach, if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current therapy • Treatment steps for children 6–11 years • Long-acting muscarinic antagonists (LAMAs) • Add-on azithromycin (adults) • Blood eosinophils for eligibility for biologic treatment	143
EAACI guidelines for the use of biologicals in severe asthma	• Follow the GRADE approach in formulating recommendations for each biological, each outcome and each age group • A management algorithm for the use of biologicals in the clinic is proposed: (i) the biological treatment decision is based on 3 pillars: phenotype, biomarkers and outcomes plus the shared decision with the patient in setting the treatment goals; (ii) the patient is evaluated after 4–6 months and classified as responder, partial responder and non-responder, according to the pre-set treatment goals; (iii) partial/non-responder patients should be further evaluated for the local inflammation (induced sputum is recommended as non-invasive tool) and for AHR; (iv) for persistent eosinophilic inflammation several options are offered starting with checking the adherence to asthma background controller treatment, to switching to a different dose and administration route, targeting another pathway and to measuring anti-drug antibodies and autoimmune biomarkers; (v) if no eosinophilic inflammation is present non-T2 asthma interventions (eg low dose macrolides) should be considered • Future approaches and research priorities are discussed	144
2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group	• Addresses six priority topic areas: a. Fractional Exhaled Nitric Oxide Testing b. Indoor Allergen Mitigation c. Intermittent Inhaled Corticosteroids d. Long-Acting Muscarinic Antagonists e. Immunotherapy in the Treatment of Allergic Asthma f. Bronchial Thermoplasty • To assist clinicians in implementing recommendations into patient care, the new recommendations have been integrated into the existing Expert Panel Report 3 (EPR-3) asthma management step diagram format	145
Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline	• Suggest using anti-IL-5 and anti-IL-5Rα for severe uncontrolled adult eosinophilic asthma phenotypes • Suggest using blood eosinophil cut-point of ≥150/μL to guide anti-IL-5 initiation in adult patients with severe asthma • Suggest considering specific eosinophil (≥260/μL) and FeNO (≥19.5 ppb) cut-offs to identify adolescents or adults with the greatest likelihood or response to anti-IgE therapy • Suggest using inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite GINA step 4–5 or NAEPP step 5 therapies • Suggest a trial of chronic macrolide therapy to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype • Suggest using anti-IL-4/13 for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels	146

with all relevant clinical, contextual, experiential and ethical data.[112] An interesting study using a cohort state-transition model (Markov model) evaluated the potential consequences in costs and health-related quality of life of the evaluated strategies in the clinical pathway of asthmatic patients over a 10-year time horizon. The results suggested that subcutaneous immunotherapy added to ICS is cost-effective compared with ICS in the reduction of exacerbations and the discontinuation of rescue and controller medications.[113]

6 | ASTHMA AND ENVIRONMENTAL SCIENCE

Several holistic and interdisciplinary approaches exist to safeguard health. Three of the most influential concepts at the moment are One Health, EcoHealth and Planetary Health.[114]

The impact of climate change on the environment, biosphere and biodiversity has become more evident in recent years. Respiratory health can be particularly affected by climate change. Pollen allergy and the duration and intensity of pollen season are altered by climate change. Mould proliferation is increased by floods. Thunderstorms during pollen seasons can cause severe asthma symptoms in patients with allergic rhinitis. A similar phenomenon is observed for moulds.[81,115] Wildfires are becoming more frequent and destructive in a changing climate. Wildfire-specific fine particulate matter PM2.5 was found to be ~10 times more harmful on children's respiratory health than PM2.5 from other sources, particularly for children aged 0–5 years.[116] The described immunological mechanism implicates IL-1β and C reactive protein.[117]

The exposome—immune system interplay is decisive for resilience and immune homeostasis.[118] Diet, microbiome and the epithelial barrier are key regulators of the cross-talk that ensures that immune system adapts to challenges by establishing, maintaining and regulating an appropriate immune response. There is a paradigm shift in prevention, from avoidance to immunological tolerance/resilience as exemplified by the first national programme for prevention (The Finnish Allergy Programme 2008–2018).[119]

A longitudinal study conducted on 1050 children from a population-based birth cohort recruited in Portugal showed that living in close proximity to a greener environment at birth had a protective effect on the development of allergic diseases and asthma at the age of 7. Conversely, living in neighbourhoods with a high number of fauna species appears to be associated with a higher risk of allergy, asthma and wheezing.[120]

7 | INTERNATIONAL ASTHMA GUIDELINES

Several asthma-related guidelines were published in the last 12 months (Table 3). As a general feature, the 'one size fits all' model is being replaced by the stratified approach for severe asthma.

8 | ASTHMA AND COVID-19 PANDEMICS

Initial studies reported a very low incidence of COVID-19 in asthma patients, including those with severe phenotypes.[121–125] These studies could be biased by the high adherence of asthma patients to COVID-19 protective measures. This finding could be explained by the fact that ICS decrease the expression of the angiotensin-converting enzyme (ACE)-2 receptor used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to invade the airway mucosa.[126] Subsequent studies on larger sample sizes showed that severe asthma is a risk factor for COVID-19-related death.[127–129]

Pulmonary function testing (PFTs) are essential for asthma diagnosis. International guidance highlights PFTs as an aerosol-generating procedure. Transmission of SARS-CoV-2 within the healthcare setting is a major concern, in particular for small droplets (typically ≤5 microns), which have been shown to contain virus, as well as remaining airborne for longer, potentially increasing spreading. Quantification of particle formation during different breathing manoeuvres using the Particles in Exhaled Air (PExA, Sweden) technique showed that exhaled small particle mass varied with different breathing manoeuvres, with very low production in tidal breathing and slow vital capacity (VC) and low production during FEV manoeuvres. Thus, spirometry, in the absence of coughing, is likely not to present a considerably higher risk in the absence of an airway closure manoeuvre prior to the VC test.[130] Sputum induction is the gold standard approach to the non-invasive study of airway inflammation. A consensus-based protocol to ensure its biosafety in clinical practice during the current COVID-19 pandemic was recently published.[131]

The pandemic significantly impaired the management of adult and paediatric asthma[132,133] and has ongoing unpredictable consequences.

Considering all challenges posed by the pandemic the EAACI-ARIA Panel issued recommendations for asthma management during the pandemic.[134]

BOX 2 Future research perspectives

- Enhanced focus on restoring the epithelial barrier in asthma is required.
- Following the description of the major subendotypes in non-T2 asthma, biomarkers facilitating targeted interventions are to be developed.
- Assess the mechanisms of asthma inception.
- The long-term effects of anti-inflammatory treatments, including biologicals.
- Tools for a quick, accurate and low-cost diagnosis of asthma endotypes and subendotypes should be prioritized.
- Holistic prevention measures following the Planetary Health model should be reinforced
- A unified approach to innovation is needed to address the challenge of asthma

9 | CONCLUDING REMARKS

Despite the well-recognized heterogeneity in asthma, several mechanisms (eg epithelial barrier dysfunction, pathways in non-T2 asthma) and treatable traits (eg bronchoconstriction) are shared by (virtually) all disease phenotypes. Therefore, the correct management of asthma patients requires an adequate balance between guideline informed severity-tailored treatment and precision medicine-based individualized approaches. Adapting clinical practice and asthma research to major provocations such as the COVID-19 pandemics, climate change or other planetary health threats is key to move the field forward (Box 2).

CONFLICT OF INTEREST

IA reports serving as Associate Editor of Allergy and CTA. **CA** reports grants and/or fees from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission Horizon 2020 Framework Programme, Cure, Novartis Research Institute, AstraZeneca, SciBase, Sanofi/Regeneron, GlaxoSmithKline, and Novartis. **MJ** reports personal fees from ALK-Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL, AstraZeneca, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, MedImmune, and Chiesi. All other authors declare no conflict of interest.

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How to cite this article: Agache I, Eguiluz-Gracia I, Cojanu C, et al. Advances and highlights in asthma in 2021. *Allergy*. 2021;76:3390–3407. https://doi.org/10.1111/all.15054