

Recent Insights into the Management of Inflammation in Asthma

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Abstract: The present prevailing inflammatory paradigm in asthma is of T2-high inflammation orchestrated by key inflammatory cells like Type 2 helper lymphocytes, innate lymphoid cells group 2 and associated cytokines. Eosinophils are key components of this T2 inflammatory pathway and have become key therapeutic targets. Real-world evidence on the predominant T2-high nature of severe asthma is emerging. Various inflammatory biomarkers have been adopted in clinical practice to aid asthma characterization including airway measures such as bronchoscopic biopsy and lavage, induced sputum analysis, and fractional exhaled nitric oxide. Blood measures like eosinophil counts have also gained widespread usage and multicomponent algorithms combining different parameters are now appearing. There is also growing interest in potential future biomarkers including exhaled volatile organic compounds, micro RNAs and urinary biomarkers. Additionally, there is a growing realisation that asthma is a heterogeneous state with numerous phenotypes and associated treatable traits. These may show particular inflammatory patterns and merit-specific management approaches that could improve asthma patient outcomes. Inhaled corticosteroids (ICS) remain the mainstay of asthma management but their use earlier in the course of disease is being advocated. Recent evidence suggests potential roles for ICS in combination with long-acting beta-agonists (LABA) for as needed use in mild asthma whilst maintenance and reliever therapy regimes have gained widespread acceptance. Other anti-inflammatory strategies including ultra-fine particle ICS, leukotriene receptor antagonists and macrolide antibiotics may show efficacy in particular phenotypes too. Monoclonal antibody biologic therapies have recently entered clinical practice with significant impacts on asthma outcomes. Understanding of the efficacy and use of those agents is becoming clearer with a growing body of real-world evidence as is their potential applicability to other treatable comorbid traits. In conclusion, the evolving understanding of T2 driven inflammation alongside a treatable traits disease model is enhancing therapeutic approaches to address inflammation in asthma.

Keywords: asthma, biologics, monitoring, respiratory disease, T2 inflammation, treatable traits

Introduction

Asthma is one of the commonest chronic conditions in the world affecting over 300 million individuals worldwide, with prevalence rates ranging from 1% to 16% in different countries.¹ It is rarely fatal, but the economic burden associated with asthma is extensive due to direct and indirect medical costs, including prescription drug costs, healthcare utilisation and productivity losses. Asthma is a heterogeneous disease usually characterised by chronic airway inflammation,¹ bronchial hyperresponsiveness and recurrent episodes of reversible airway obstruction. Airway inflammation is a hallmark of asthma and underscores many of the

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pathophysiological changes seen within the asthmatic airways resulting in the characteristic symptoms of asthma, such as wheeze, shortness of breath, chest tightness and cough.

Asthma management guidelines are based on a step-wise approach with treatment progressively increased to achieve asthma symptom control and reduce risk of exacerbations, with the option to reduce treatment doses after a period of symptom control. While asthma is recognised as comprising various disease subtypes, it is now frequently categorised into type 2 high (T2-high) and type 2 low (T2-low) asthma based on the predominance of cytokines and their cellular sources. Most asthma treatments target inflammatory pathways within the lung to help improve symptoms, reduce risk of exacerbations and avoid long-term complications. However, it is increasingly recognised that other treatable traits overlap with asthma and can contribute to poor symptom control in asthma.

In this review, we highlight advances in managing inflammation in asthma through the lens of the T2 paradigm alongside other relevant emerging concepts such as the “Treatable Traits” model for more complex asthma. We will review new perspectives on conventional treatments, evolving monitoring processes and current, plus potential future, higher-level biologic treatments with a focus on real-world data and clinical applicability.

The Present-Day T2 Paradigm of Inflammation in Asthma

Asthma is a heterogeneous chronic inflammatory airway disease comprising numerous phenotypes (observable clinical characteristics) and their underlying endotypes (biological pathways). The asthma disease model has evolved considerably since Rackemann first described “intrinsic” and “extrinsic” disease forms over 70-years ago.² Morrow Brown’s findings in the 1950’s that sputum eosinophilia determined response to oral and inhaled corticosteroids further focused attention on the role of eosinophils in asthma pathophysiology.³ With time, associations between airway eosinophilia and more severe airway remodelling changes plus worse clinical outcomes became evident.⁴ Thereafter evolved the concept of “T2-high” and “T2-low” asthma inflammatory endotypes⁵ defined by the presence or absence of Type 2 (T2) inflammatory processes. T2 inflammation may be orchestrated by either (CD4+) Type 2 helper (Th2) lymphocytes or innate lymphoid cells group 2 (ILC2).⁶ Th2 lymphocytes elaborate cytokines

that have critical “asthma-genic” actions including interleukin (IL)-4, IL-5 and IL-13. IL-4 promotes production of IgE from B lymphocytes, increases expression of low-affinity CD23 (Fc ϵ R2) IgE receptors on B lymphocytes and macrophages while directing class switching of naïve CD4 T-helper lymphocytes to the T2 type.⁷ IL-13 shares a common receptor (IL-4R α) with IL-4 and shows similar effects including promoting IgE production and CD23 expression.^{8,9} IL-4 and IL-13 also induce goblet cell metaplasia and MUC5AC production, favouring mucus production in the asthmatic airway.⁹ IL-5 is a key driver of eosinophilic processes, responsible for eosinophil migration into the asthmatic airway where they are a predominant cell type in T2 disease.¹⁰ Eosinophils therefore remain a prime target for a range of evolving asthma treatment options from newer inhaled corticosteroids and other prophylactic medications to monoclonal antibody biologic treatments. In parallel, blood eosinophil count (BEC) has gained widespread acceptance as a surrogate of airway pathophysiology. Conversely, non-eosinophilic and non-T2 phenotypes potentially less responsive to conventional and higher-level biologic treatments have been described too.¹¹ However, defining non-T2 asthma largely by the absence of T2 features potentially leaves room for misclassification. For instance, it is known that BEC show considerable temporal variability and alongside other T2 markers such as Fractional Exhaled Nitric Oxide (FeNO) are susceptible to numerous modifying factors including treatments.¹² Neutrophilic airway inflammatory profiles have long been linked to severe asthma and may constitute a proportion of non-T2 asthma.¹³ They can be facilitated by IL-17 mediated pathways which have also been linked to severe asthma.^{14,15} Paucigranulocytic (low) airway inflammatory profiles may comprise a further proportion of non-T2 asthma.¹⁶ Systemic inflammation in association with metabolic dysfunction and obesity has also been linked to non-T2 asthma.¹⁷

How does the T2 paradigm relate to asthma encountered in clinical practice? The Global Initiative for the management of Asthma (GINA) proposed a multidimensional algorithm to define T2 status – any of BEC \geq 150 cells/ μ L, sputum eosinophilia \geq 2%, FeNO \geq 20ppb, clinically allergy-driven asthma, or on maintenance oral corticosteroids for asthma.¹⁸ GINA estimated that 50% of severe asthma is T2 in nature.¹⁹ In line with that estimate, recent data from UK-SAR (the United Kingdom Severe Asthma Registry) classified 45% of subjects as T2 when that was defined as both BEC \geq 150 cells/ μ L and FeNO \geq

25ppb.²⁰ However, emerging real-world data using broader perspectives suggests a greater extent of T2 status among patients with severe asthma.

Heaney et al recently reported findings within ISAR, the International Severe Asthma Registry²¹ using data on 1716 patients from 11 national registries. They applied a consensus-driven eosinophil gradient algorithm to assess eosinophilic phenotypes in severe asthma classifying eosinophilic status from Grade 3 (most likely eosinophilic), Grade 2 (likely eosinophilic), Grade 1 (least likely eosinophilic) to Grade 0 (non-eosinophilic). The variables selected to inform the algorithm were: highest BEC ever (≥ 300 , ≥ 150 – 300 , < 150 cells/ μ L), anti-IL-5/IL-5R (eosinophil targeting) biologic treatment, long-term oral corticosteroid ever (m-OCS), elevated FeNO ever (≥ 25 ppb), nasal polyps diagnosis ever, and adult-onset asthma (≥ 18 -years). Non-eosinophilic status was defined as highest BEC ever < 150 cells/ μ L without nasal polyps, elevated FeNO, adult-onset asthma or m-OCS. Conversely, Grade 3 (most eosinophilic likelihood) was defined as either highest BEC ever ≥ 300 cells/ μ L OR anti-IL-5/IL-5R therapy, OR with BEC ≥ 150 – 300 cells/ μ L on (i) m-OCS or (ii) with ≥ 2 of nasal polyps, elevated FeNO or adult-onset disease. Using this approach, eosinophilic phenotypes heavily predominated in severe asthma with 83.8% of subjects falling into “most likely” eosinophil phenotypes and only 1.6% falling into non-eosinophil phenotypes. Supporting evidence for such levels of eosinophilic/T2 disease comes from recently published UK data from the Wessex AsThma CoHort of difficult asthma (WATCH) study.²² That real-world study used historical electronic health records to longitudinally study blood eosinophil status in difficult asthma patients over a 10-year period. It found that while 40.3% showed BEC ≥ 300 cells/ μ L at WATCH enrolment, this proportion rose to 83.4% when viewed longitudinally. Furthermore, if the BEC cut-off was dropped to ≥ 200 cells/ μ L, the prevalence of “eosinophilia ever” rose to 96.6%.

How do eosinophilic and non-eosinophilic severe asthma phenotypes differ in core characteristics and clinical outcomes? Most severe asthma cohorts show female predominance.^{21,23–25} While ISAR confirmed that, it showed proportionately greater prevalence of male sex in the eosinophilic than in the non-eosinophilic group.²¹ The eosinophil group were both older and had older age of asthma onset echoing recent identification in the WATCH study of a hitherto less acknowledged adult-onset eosinophilic male difficult asthma phenotype.²³ The ISAR study

found no significant difference in numerous asthma characteristics including severity between eosinophilic and non-eosinophilic phenotypes.²¹

Collectively, these real-world studies suggest exercising caution before designating non-eosinophilic severe asthma status. Eosinophil-phenotype predominance in severe asthma highlights that most severe asthma patients fall within the remit of T2-biologics such as Omalizumab, Mepolizumab, Reslizumab, Benralizumab and Dupilumab which are transforming treatment options for many patients with asthma. It is though important to recognise that some patients don't respond to T2-biologics as recently shown by real-world studies like WATCH.²⁶ Understanding the mechanisms behind such failed responses will be a matter for future research focus.

Biomarkers That Support Asthma Management

The diagnosis and management of asthma is generally based on a combination of reported symptoms and lung function tests that assess reversible airway obstruction and airway hyperresponsiveness (AHR). However, these do not directly reflect underlying airway inflammation and cannot discriminate different phenotypes. Therefore, biomarkers that can reflect airway inflammation are needed to guide diagnosis, help accurately identify clinically relevant phenotypes, guide treatment decisions and potentially also inform prognosis. In this section, we present an overview of asthma biomarkers and discuss their advantages plus barriers to their implementation. We have focused on adults with asthma but similar biomarkers are used in the paediatric population. The advantages and disadvantages of currently used clinical biomarkers are summarized in Figure 1.

Airway Sampling Though Bronchoscopy

Bronchial biopsy, obtained through fiberoptic bronchoscopy, was first used for research purposes in asthma in 1977.²⁷ Since then, many have considered bronchial biopsy the “gold standard” for investigating airway inflammation because it enables detailed study of the epithelium, basement membrane and submucosa, allows quantification of inflammatory cells and permits evaluation of their activation status. Bronchial biopsies from patients with asthma often show epithelial shedding, goblet cell hyperplasia, thickened lamina reticularis, increased inflammatory cells (especially eosinophils) and basement membrane thickening, a hallmark of airway remodelling.^{28,29} Bronchial

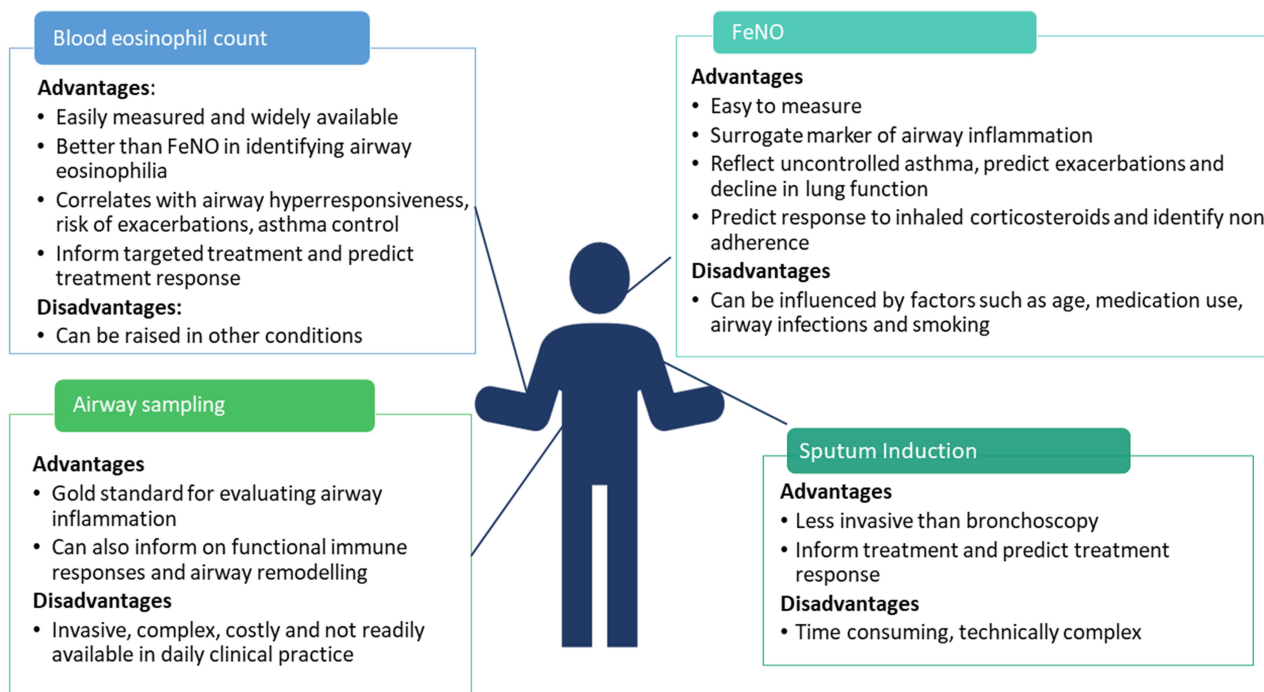


Figure 1 Advantages and disadvantages of commonly used asthma biomarkers.

Abbreviation: FeNO, fractional exhaled nitric oxide.

brushings, also obtained through bronchoscopy provide bronchial epithelial cells which can be harvested and cultured in vitro. Bronchial epithelial cells are key producers of inflammatory and immune mediators and these in vitro studies have greatly advanced our understanding of the inflammatory and immune responses within the asthmatic airway. Finally, bronchoalveolar lavage, performed during bronchoscopy, allows for analysis of inflammatory cells, cytokines and other soluble mediators from the distal airways. However, while bronchoscopy has contributed significantly to the enhanced understanding of asthma, it is invasive, complex, costly to perform, not readily available in daily clinical practice and therefore remains mainly a research tool.

Sputum Induction

Sputum induction is less invasive and more-cost-effective than bronchoscopy but remains time-consuming, technically complex and requires specialist resource, preventing its widespread use in routine clinical practice. Four inflammatory phenotypes have been identified based on analysis of sputum: eosinophilic, neutrophilic, mixed and paucigranulocytic.³⁰ The number of eosinophils in sputum from asthmatic patients is significantly raised compared with healthy people and correlates with severe

exacerbations and AHR.³¹ Sputum eosinophil guided treatment of patients with moderate to severe asthma is associated with fewer severe asthma exacerbations and fewer hospital admissions compared to management based on symptoms and clinical assessment alone.³² Using sputum eosinophilia to guide asthma medication cannot be extended to children due to the lack of sufficient data.³³

Studying sputum inflammometry in patients with severe asthma has been a focus for many years. The Severe Asthma Research Program III (SARP III) recently reported data from 206 subjects with severe asthma that shows the majority (59%) have low eosinophils (<2%) in sputum. Similarly, in the Wessex Severe Asthma Cohort, the majority of the 210 participants (59%) had low sputum eosinophils ($\leq 3\%$)³⁴ albeit the cut-offs used varied slightly between the two cohorts. It is also recognised that levels of inflammatory cells in sputum vary over time and with treatment. Variable levels of sputum eosinophilia were found in 15% of patients in SARP III over a 3-year period. Such patients had the highest rate of exacerbations despite being on greater treatment, higher even than patients with persistently raised sputum eosinophilia. This highlights that fluctuation in sputum eosinophil count is more closely linked to asthma control than the absolute levels of these inflammatory cells.

Fractional Exhaled Nitric Oxide

Nitric oxide (NO) is a gas normally found in exhaled breath and at constitutive levels has numerous regulatory and immunomodulatory roles.³⁵ Using a hand-held analyser, the fraction of NO in exhaled breath (FeNO) can be measured in a convenient, non-invasive and reproducible manner, making it a valuable clinical tool. Within the asthmatic airway, T2 cytokines upregulate the production of nitric oxide.^{36,37} High FeNO levels are therefore thought to be a surrogate marker of ongoing airway inflammation and may reflect uncontrolled asthma, predict asthma exacerbations³⁸ and decline in lung function.^{39,40}

However, the clinical usefulness of FeNO is still debated, mainly because various other factors can influence FeNO levels such as age, medication use, airway infections, smoking status and other diseases including eosinophilic bronchitis. This probably explains why studies investigating the association between FeNO and asthma control provide inconsistent results.⁴¹

FeNO >50ppb can predict response to inhaled corticosteroid therapy (ICS)^{42,43} and in patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS. Levels are also responsive to changes in ICS⁴⁴ and the degree of suppression of FeNO resulting from ICS therapy has been used to identify non-adherence to this treatment in a difficult-to-treat asthma population.⁴⁵ However, outside of this group of patients, the evidence is low and therefore the National Asthma Education and Prevention Coordinating Committee (NAEPPCC) 2021 recommends against the routine use of FeNO to evaluate adherence.⁴⁴ While a management strategy involving FeNO guided treatment adjustment has been shown to be associated with a significantly reduced exacerbation risk (OR 0.60; 95% CI 0.43–0.84 in adults and OR 0.58; 95% CI 0.45–0.75 in children) in a recent meta-analysis,⁴⁶ international guidelines are cautious with their recommendations. GINA advises against FeNO-guided adjustment to asthma treatment while the NAEPPCC makes a conditional recommendation that FeNO can be used in conjunction with usual clinical parameters including history, clinical findings and spirometry.^{1,44}

FeNO can modestly predict airway eosinophilia with a recent meta-analysis suggesting an area under the receiver operator curve (AUROC) for detecting sputum eosinophils $\geq 3\%$ of 0.75 (95% CI 0.72–0.78), sensitivity of 66% (95% CI 57–75%) and specificity of 76% (95% CI 65–85%).⁴⁷ However, clinical experience with FeNO has shown that

while T2-inflammation and airway eosinophilia may overlap, they are not synonymous. This distinction has been clearly demonstrated with the use of anti-IL5 (Mepolizumab) and anti-IL4R α (Dupilumab) monoclonal antibodies. Mepolizumab use leads to significant reductions in peripheral blood eosinophil levels without any change in FeNO while Dupilumab reduces FeNO without affecting blood eosinophil levels.^{48,49}

Biomarkers in Blood

Blood Eosinophil Count

BEC is easily measured and widely available, with the added advantage that patients often have a standard full blood count checked for various reasons and therefore a recent (or historical) BEC is usually available. They reflect inflammation in the asthmatic airway and are better than FeNO in the identification of sputum eosinophilia in asthma (AUROC for BEC 0.89 while for FeNO 0.78).⁵⁰ Eosinophils correlates with AHR and rate of decline in FEV₁ in younger and older adults, independent of the presence of asthma.^{51,52} They are useful in the early detection of exacerbations. Large intervention studies in patients with mild, moderate and severe asthma show that the BEC is independently associated with up to a fivefold increased risk for severe exacerbations.^{48,53,54} They correlate with asthma control⁵⁵ and can inform targeted treatment and predict treatment response, especially to asthma biologics in adults and children.^{48,49,56,57} However, the utility of BEC is limited by low overall specificity for eosinophilic airway inflammation⁵⁸ as raised BEC can be seen in other autoimmune diseases, atopic diseases and parasitic infections.

Serum Periostin

Periostin is a matricellular protein secreted by bronchial epithelial cells and fibroblasts under the influence of IL-13.⁵⁹ Gene expression studies show that it is amongst the most highly expressed genes in the T2 high population⁵ and it is considered a biomarker of T2, IL-13 driven steroid-responsive asthma.⁶⁰ However, correlation between serum periostin and sputum eosinophilia is inconsistent. While the BOBCAT study showed it was predictive of eosinophilic airway inflammation with an AUROC of 0.84,⁶¹ in another study, periostin was unable to distinguish eosinophilic asthma from non-eosinophilic asthma.⁵⁰ However, the use of this biomarker is limited by the lack of well-established and validated cut-off values and standardised measurement techniques that can be employed in routine clinical care.

Periostin levels can change with age and affected by bone growth and turnover—this is particularly relevant in children. Therefore, the usefulness of serum periostin in children is still debated and largely due to inconsistencies in results.

Combining Biomarkers

Combining FeNO levels with BEC may add additional discriminatory value in predicting exacerbations and response to treatment. Price et al demonstrated that primary care patients with FeNO > 50 ppb and BEC > 300 cells/μL were almost four times as likely to have a severe exacerbation compared to biomarker low patients.⁴³ Recently, a group in Oxford have proposed the ORACLE score (Oxford Asthma attack risk scale) which can predict asthma attacks based on these two biomarkers combined with concurrent risk factors including poor symptom control, low lung function, adherence issues and reliever over-use.⁶² Combined biomarker high patients also respond better to certain, but not all, biologic treatments⁴⁸ highlighting the heterogeneity in airway inflammation in asthma. As described above, recently, the ISAR proposed an algorithm to predict an eosinophilic phenotype based on BEC and FeNO combined with select clinical characteristic highlighting the benefit of combining clinically available biomarkers.²¹

Future Biomarkers to Aid Management of Inflammation in Asthma

The ideal biomarker should have good performance characteristics, such as sensitivity, specificity, positive-predictive and negative predictive values. Furthermore, it should be simple to measure and cost-effective.⁶³ So what candidates might fit that bill for future use as asthma biomarkers? It is beyond the scope of this Review to undertake detailed assessment of future biomarkers that could prove useful in guiding management of inflammation in asthma. Here, we briefly highlight 3 promising candidates.

MicroRNAs

MicroRNAs (miRNAs) are short, single-stranded RNA molecules, 18–22 nucleotides long and highly conserved throughout evolution⁶⁴ that have been associated with particular asthma phenotypes.⁶⁵ Several studies reported correlations between miRNAs and asthma phenotypes, for example, several miRNAs have been linked to T2 asthma including miR-155, miR-146a, miR-21, miR-1248, miR-210 and miR-1.^{66,67} Other miRNAs have been linked to neutrophilic asthma

including miR-199a-5p, miR-223-3p, miR-142-3p and miR-629-3p.⁶⁸ Additionally, miR-1 level was found to be inversely correlated with asthma severity.⁶⁷ Another study, showed that expression levels of miR-125b in serum exosomes were significantly different among patients with intermittent, mildly, moderately, and severely persistent asthma having a high diagnostic efficacy for asthma severity.⁶⁹ A set of miRNAs were recently associated with asthma that could also classify asthmatics into two clusters by serum eosinophil numbers and periostin concentration. Some of these asthma-specific miRNAs have been identified in sera, including miR-185-5p.⁷⁰ In neutrophilic asthma, miR-199a-5p, miR-223-3p, miR-142-3p and miR-629-3p were upregulated in induced sputum. miR-629-3p was expressed in bronchial epithelium and miR-223-3p and miR-142-3p—in neutrophils, monocytes and macrophages.⁶⁶ Such biomarkers could therefore have a future potential to aid endotypic recognition at individual patient levels and facilitate future stratified medicines approaches.

Exhaled Volatile Organic Compounds

Exhaled volatile organic compounds (VOCs) include a wide range of potential substances such as alkanes, hydrocarbon ring structures, alcohols, aldehydes, aromatic hydrocarbons and ketones. They offer a means to non-invasively examine airway inflammatory status and phenotype in line with the concept of distinguishing treatable traits. Such “breathomic” analyses both via broad-ranging platforms such as e-Nose as well as more targeted gas chromatography-mass spectrometry have identified eosinophil and neutrophilic phenotypes of airway disease distinguished by exhaled breath constituents (such as 3,7-dimethylnonane, nonanal and 1-propanol) rather than predetermined diagnostic labels.^{71,72} They have also demonstrated differences in exhaled VOCs such as methanol, acetonitrile, and bicyclo [2.2.2]octan-1-ol, 4-methyl between stable and uncontrolled asthma status.⁷³ Conversely, other studies have failed to show such clear breathomic signatures.⁷⁴ Further work to validate these early findings is needed but initial systematic reviews suggest promise to this potential VOC-based biomarker approach.⁷⁵

Urinary Biomarkers

Urinary biomarkers have also attracted recent interest in relation to asthma. T2 status has been associated with raised urinary metabolites of prostaglandin D₂ and cysteinyl-leukotriene (LT) E₄ with equivalent accuracy to

conventional markers.⁷⁶ Urinary LTE₄ has also shown potential as a marker for AERD.⁷⁷ Conversely, an IL-17 high asthma phenotype has been associated with elevated urinary degradation products of thromboxane B₂ that might serve as a biomarker for future attempts at IL-17 targeted therapy.⁷⁸ Urinary bromotyrosine in combination with FeNO was also found to best predict clinical inhaled corticosteroid response.⁷⁹ Urinary biomarker guided asthma management is therefore likely to be an area of growing research focus.

The Treatable Traits Paradigm – Difficult-to-Control Asthma as a Multimorbidity Difficult Breathing Syndrome

Our current pharmacotherapeutic approach to asthma is moulded to the T2 paradigm. Yet clinical studies show wide heterogeneity to asthma both across the life course and at different levels of asthma severity.^{25,80–82}

It is also clear that a proportion of patients with asthma do not attain good asthma control with current treatments. This failure to deliver good asthma control with current approaches was the focus of a Lancet 2017 Commission “After asthma: redefining airways disease”.⁸³ In addition, the realisation is dawning that asthma seldom occurs as an isolated health problem. In particular at the more “difficult-to-control” end of the spectrum asthma often constitutes part of a multimorbidity constellation of conditions best regarded as a “Difficult Breathing Syndrome” rather than “Severe Asthma” alone. An important new taxonomic approach to airways disease based on identifying and managing component factors rather than generic disease labels such as asthma was recently proposed by Agusti.⁸⁴ Such potentially modifiable factors, known as “treatable traits” may be broadly categorised as pulmonary, extrapulmonary and behavioural in nature and occur concurrently in combinations that are specific to the individual patient. A core tenet of this framework is to acknowledge the underlying biological complexity of clinical presentations in a manner that facilitates more precise asthma management that is more personalised and holistic (Table 1). That shifts thinking away from the “one approach suits all” attitude encouraged by traditional guideline-based management.

Treatable traits are common in difficult-to-treat, asthma where they may cluster to a greater degree in individual patients.^{85–88} Of note, the burden of treatable traits appears to align with worse asthma outcomes such as

exacerbations, asthma control and quality of life.^{85,87,88} A systematic clinical approach to addressing treatable traits in asthma has recently shown clinical effectiveness.⁸⁹ So how can addressing specific treatable traits impact airway inflammation in asthma and asthma outcomes? A broad overview of treatable traits in asthma is provided in Table 1. Selected examples are further discussed below while specific treatments are assessed in subsequent sections of this Review.

Pulmonary Traits

Airway Inflammatory Phenotypes

Airway eosinophilia is defined by elevated sputum eosinophils ($\geq 2\%$) or surrogate markers such as FeNO (≥ 25 ppb).¹⁸ Although conventionally responsive to inhaled and/or oral corticosteroids, eosinophilic asthma phenotypes may prove more difficult-to-treat and have emerged as dominant in the severe asthma population.^{21,22} Patients who do not respond to conventional therapies should have multi-disciplinary team input including management of any comorbidities and optimisation of adherence and inhaler technique before resorting to higher-level biologic strategies. It is worth noting that the evolution of anti-IL5 therapy itself demonstrated the value of a treatable traits approach. When first assessed clinically without stratification by eosinophil phenotype it showed limited efficacy,⁹⁰ only to demonstrate clinical impact when trialled in patients with clear eosinophilic status.^{91,92} Neutrophilic airway inflammation is variably defined by sputum neutrophils ($\geq 40\%$ or $\geq 61\%$) and has been linked to asthma severity through worse lung function, relative corticosteroid resistance and high healthcare utilisation.^{13,93–95} It may be associated with smoking, pollutants and repeated infections which merit attention as associated treatable traits.^{96–98} Macrolide antibiotics offer potential anti-inflammatory treatment for this phenotype.⁹⁹ Mixed inflammatory airways disease is characterised by dual eosinophil and neutrophilic airway inflammation and may show worse lung function and asthma outcomes including exacerbations and healthcare utilisation.^{99,100} Conversely, paucigranulocytic airway disease is characterized by a combination of low sputum eosinophils and neutrophils. In some cases, this may reflect the effect of treatments on airway inflammatory profiles and has been linked to less severe disease status.^{16,101} No bespoke treatment exists for paucigranulocytic airways disease but there is speculation that long-acting bronchodilators and bronchial thermoplasty may offer some utility.¹⁰² While airway inflammatory status is a key treatable trait, the longitudinal stability of such asthma endotypes remains unconfirmed.¹⁰³ Both treatment

Table I Treatable Traits in Asthma; Evaluation and Management Options

	Trait	Diagnostic Evaluation	Management Options
Pulmonary	Airflow Limitation	Spirometry with FEV ₁ /FVC <0.7	Inhaled corticosteroids, long acting β_2 agonists, long-acting antimuscarinic agents.
	Small Airways Disease	Impaired FEF _{25–75} , impaired oscillometry, evidence of air-trapping on plethysmography \pm HRCT.	Ultrafine particle inhaled corticosteroids.
	Airway Inflammatory Phenotype (Eosinophilic, Mixed)	Sputum eosinophils (%), blood eosinophil count, FeNO	Inhaled corticosteroids, leukotriene antagonists, oral corticosteroids, monoclonal antibody therapies.
	Airway Inflammatory Phenotype (Neutrophilic)	Sputum neutrophils (%)	?Long-acting antimuscarinic agents, ?prophylactic antibiotics, ? bronchial thermoplasty.
	Airway Inflammatory Phenotype (Paucigranulocytic)	Sputum eosinophils and neutrophils (%)	?Long-acting antimuscarinic agents, ?prophylactic antibiotics, ? bronchial thermoplasty.
	Allergic Fungal Airway Disease	Total IgE, specific IgE to Aspergillus, Aspergillus Precipitins, HRCT chest.	Inhaled/ oral corticosteroids, antifungal agents, monoclonal antibody therapies.
	Aspirin Exacerbated Respiratory Disease	Clinical history & examination, aspirin challenge	Aspirin desensitisation, salicylate lowering diet, inhaled corticosteroids, leukotriene antagonists, oral corticosteroids, monoclonal antibody therapies.
	Airway Infections \pm Colonisation	Clinical history, antibiotic history, sputum culture.	Acute/ prophylactic antibiotics.
	Bronchiectasis	Clinical history & examination, HRCT, sputum culture.	Chest clearance, prophylactic antibiotics, nebulised antibiotics.
	Dual COPD	Clinical history & examination, spirometry, transfer factors, HRCT, sputum culture.	Smoking cessation, chest clearance, pulmonary rehabilitation, long acting β_2 agonists, long-acting antimuscarinic agents.
Extra-Pulmonary	Rhinitis	Clinical history & examination,	Topical nasal steroids, antihistamines, leukotriene antagonists, nasal rinses, allergen immunotherapy.
	Chronic Rhinosinusitis (\pm Nasal Polyps)	Clinical history & examination, nasendoscopy, CT sinuses.	Topical nasal steroids, antibiotics, nasal rinses, surgery.
	Gastro-Oesophageal Reflux Disease	Clinical history & examination, upper GI endoscopy, pH monitoring.	Proton pump inhibitors, H2 antagonists, weight loss, surgery.
	Obesity	Body Mass Index	Diet, exercise, medication, bariatric surgery.
	Deconditioning	Clinical history, 6 Minute Walk Test	Exercise.
	Obstructive Sleep Apnoea	Clinical history & examination, Epworth Sleepiness Score, sleep study.	Weight loss, mandibular advancement devices, Continuous Positive Airways Pressure therapy.
	Dysfunctional Breathing	Clinical history & examination, Nijmegen score.	Physiotherapy support.
	Intermittent Laryngeal Dysfunction	Clinical history & examination, indirect laryngoscopy.	Speech therapy support.
	Depression	Clinical history & examination, HADS score.	Psychologist support.
	Anxiety	Clinical history & examination, HADS score.	Psychologist support.

(Continued)

Table I (Continued).

	Trait	Diagnostic Evaluation	Management Options
Behavioural	Smoking	Clinical history, exhaled carbon monoxide, urinary cotinine.	Smoking cessation support, nicotine replacement therapy.
	Adherence	Clinical history, prescription pick up data, “smart inhalers”, prednisolone assay.	Patient education, motivational interviewing, self-management guidance.
	Poor Inhaler Technique	Direct assessment.	Patient education.
	Distorted Symptom Perception	Comparison of objective and subjective measures.	Patient education, treatment of relevant psychophysiologic traits.

Abbreviations: FEV₁/FVC, forced expiratory volume in 1 second/ forced vital capacity ratio; FEF_{25–75}, mid-expiratory flow; HRCT, High-Resolution CT; FeNO, fractional exhaled nitric oxide; COPD, Chronic Obstructive Pulmonary Disease; CT Sinus, Computed Tomography Sinus; GI, Gastrointestinal; HADS, Hospital Anxiety and Depression Score.

(corticosteroid escalation or weaning) plus external factors like smoking and infection might influence inflammatory phenotype status at single timepoints signalling the need to consider re-evaluation if clinical status changes.

Allergic Bronchopulmonary Aspergillosis/ Severe Asthma with Fungal Sensitisation

Sensitization to fungal allergens like *Aspergillus fumigatus* (*A. fumigatus*) has been associated with worse asthma severity through states like “Severe Asthma with Fungal Sensitization” (SAFS) and Allergic Bronchopulmonary Aspergillosis (ABPA).^{104,105} Notably, *A. fumigatus* sensitization has been linked to poor asthma control, higher treatment needs, greater healthcare utilization, potential mortality risk, impaired lung function and bronchiectasis.^{106–112} ABPA shows a specific mixed inflammatory pattern^{106,113} and classical cyclical pattern of exacerbation and worsening airway structural damage if untreated.⁴² Potential anti-inflammatory treatments include antifungal treatments, oral and inhaled corticosteroids, and consideration of higher-level biological agents.^{114–116}

Aspirin-Exacerbated Respiratory Disease (AERD)

Aspirin-sensitive asthma is typically adult-onset, with higher prevalence in females plus associations to chronic rhinosinusitis with nasal polyps (CRSwP) and chronic spontaneous urticaria.¹¹⁷ AERD is associated with baseline dysregulated arachidonic acid metabolism, heightened leukotriene responses, subdued prostaglandin E₂ production and an eosinophilic phenotype.^{118,119} Conventional treatments including inhaled corticosteroids and leukotriene antagonists may prove useful but such patients often show progressive worsening of asthma control and

increasing oral corticosteroid dependency.^{117,119} Adjunct treatments include aspirin desensitisation, salicylate lowering diets and nasal polypectomy.^{120–122} Given their underlying eosinophilic phenotype, AERD patients may benefit from T2-targeting biologic agents.¹²³

Extrapulmonary Traits Rhinitis

Mutually detrimental co-expression of asthma and rhinitis as a “unified airways disease” arising from homologous local inflammation plus secondary immunological messaging across upper and lower airway is well recognised.^{124,125} Such bidirectional severity associations may be established in childhood and potentially track along the life-course.¹²⁶ Rhinitis therapy can reduce asthma symptom burden in mild asthmatics but similar impact in more severe asthma is lacking evidence.¹²⁷ Potential rhinitis therapies that might impact comorbid asthma include antihistamines, nasal corticosteroids, leukotriene antagonists, nasal rinses and immunotherapy though the latter is contraindicated in poorly controlled asthma.¹²⁸

Chronic Rhinosinusitis (CRS)

CRS with (CRSwP) or without nasal polypsis (CRSsNP) is strongly associated with asthma, worse asthma control and shows similar T2-based inflammatory signatures.^{129–131} Some CRS subjects demonstrate perpetuation of chronic inflammation via staphylococcal nasal mucosal colonisation whereby staphylococcal Enterotoxin-B acts as a superantigen to drive local IgE formation.¹³² Current treatments for CRSwP/ CRSsNP that might aid the patient with comorbid asthma include nasal corticosteroids, nasal rinses, antibiotics (particularly doxycycline given anti-staphylococcal coverage) and surgical polypectomy to debulk inflamed tissue while a

potential role for monoclonal antibody therapies in CRSwP is emerging.¹³³ CRS therapy can improve asthma control, oral corticosteroid dependency and healthcare utilisation.^{134–136}

Obesity

Obesity is highly prevalent among difficult asthma populations^{23,25,80} and is associated with worse asthma severity.¹³⁷ The negative impact of obesity on asthma may be part-mediated by mechanical effects on lung function.¹³⁸ Additionally, obesity may be associated with neutrophilic airway inflammation, increased adipokine expression and manifestations of systemic inflammation.^{139–142} IL-6 may play a significant role in subtypes of obese asthma and offer a future therapeutic target.¹⁷ Obesity-targeting measures like conventional weight loss, broader lifestyle changes and bariatric surgery have shown efficacy in improving clinical asthma outcomes and some markers of systemic and local inflammation.^{143–146}

Behavioural Traits

Smoking

Smoking remains prevalent in asthmatics and impairs response to anti-inflammatory medications like inhaled corticosteroids.^{147,148} Smoking cessation can rapidly improve lung function and reduce airway neutrophilia in asthmatic patients but may require personalised and novel approaches.^{149,150}

Adherence

Non-adherence to asthma medication is frequent among the difficult asthma population and a significant reason for ongoing airway inflammation.^{151,152} Assessment of non-adherence is difficult and a single gold standard measure does not exist but traditional measures have included FeNO monitoring and prednisolone assays.¹⁵³ Emerging tools include remote inhaler monitoring, remote FeNO suppression tests, using simplified dosing regimes where possible and use of interactive digital technologies.^{154–158}

Conventional Anti-Inflammatory Asthma Treatments

Asthma is a chronic inflammatory disease of the airways and therefore anti-inflammatory treatment is the mainstay of asthma management. The aim of treatment is to reduce symptom burden (ie, good symptom control while maintaining normal activity levels) and minimise the risk of adverse events such as exacerbations, fixed airflow obstruction and treatment side effects.¹ Treatment

guidelines recommend a stepwise approach with progression to the next step recommended when control is not achieved or is lost at the current step. A comparative overview of three commonly used guidelines is given in Table 2.

Inhaled Corticosteroids (ICS) Therapy

Up until recently, asthma treatment guidelines recommended as required short-acting beta-agonists (SABAs) as first-line treatment for patients with mild asthma, adopting an approach that aimed to control symptoms. If symptoms persisted, treatment was stepped up and ICS therapy was initiated. This approach stemmed from the dated idea that asthma symptoms are related to bronchoconstriction (caused by bronchial smooth muscle contraction) rather than a condition concomitantly caused by airway inflammation¹⁵⁹ and therefore as required SABA monotherapy (which relaxes airway smooth muscle) is sufficient in “mild” asthma when symptoms are infrequent. However, while symptoms experienced by patients with mild asthma may not be troublesome or frequent, airway inflammation is usually present. Between 30% and 40% of exacerbations requiring emergency care have been shown to occur in patients with mild asthma.¹⁶⁰ Asthma exacerbations are associated with considerable morbidity, progressive decline in lung function and are an important predictor of future exacerbations.¹⁶¹ Therefore, in 2019 GINA guidelines changed to no longer recommend treatment with SABA alone, even in patients with mild asthma.¹

This change can be considered as revolutionising the management of patients with mild asthma and was based on evidence that had been available for some years. Firstly, it had been recognised that although SABAs effectively reduce symptoms, they are ineffective in treating the underlying inflammatory process. Patients treated with SABA alone are at risk of asthma-related death¹⁶² and urgent asthma-related healthcare utilisation¹⁶³ - both are reduced with regular use of ICS. In fact, Suissa et al showed a clear inverse dose-dependent relationship between number of ICS canisters used in a year and the rate ratio for death from asthma.¹⁶² The benefit of using ICS at step 1/mild asthma was further reinforced in 2006 when the results of a 10-year asthma programme in Finland was published. Through a comprehensive educational programme for primary care that focused mainly on the premise that asthma is an inflammatory disease and requires anti-inflammatory treatment from the outset, the

Table 2 Comparison of Adult Asthma Chronic Management Guidelines

	Global Initiative for Asthma 2021	National Asthma Education and Prevention Program Guidelines 2021	British Thoracic Society Guidelines 2019
	Non Applicable	Intermittent Asthma: PRN SABA	Suspected Asthma: Can Consider Monitored Initiation of Low Dose ICS
“Step” 1	As-needed low dose ICS/formoterol OR ICS used at the same time as SABA	Regular low dose ICS + PRN SABA OR ICS used at the same time as SABA	Regular low dose ICS + PRN SABA
“Step” 2	As needed low dose ICS/formoterol OR Regular low dose ICS + PRN SABA	Regular and as required low dose ICS/ formoterol	Regular low ICS/LABA + PRN SABA OR Low dose maintenance and reliever ICS/LABA
“Step” 3	Low dose maintenance and reliever ICS/ formoterol OR Low dose maintenance ICS/LABA + PRN SABA	Regular and as required medium dose ICS/formoterol	Medium dose ICS/LABA +PRN SABA OR Low dose ICS/LABA + LTRA +PRN SABA
“Step” 4	Medium dose maintenance ICS/ formoterol + as needed low dose ICS- formoterol OR Medium/high dose maintenance ICS/ LABA + PRN SABA	Daily medium-high dose ICS/LABA + LTRA or LAMA + PRN SABA Consider adding asthma biologic	Refer patient to specialist care for consideration of specialist therapies (including asthma biologics)
‘Step’5	Add LAMA Consider high dose ICS/formoterol OR Add on LAMA, consider high dose ICS/ LABA Refer for consideration of asthma biologic	Daily high-dose ICS/LABA + PRN SABA + OCS Consider adding asthma biologic	

Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting beta-agonist; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRN, As needed.

use of ICS increased from 33% to 85% with a parallel decrease in asthma-related hospital admissions and days off work.¹⁶⁴

However, given the low frequency of symptoms in mild asthma, patient’s adherence to regular ICS is usually low.^{165–167} This can result in SABA overuse, especially if SABAs are available in pharmacies as non-prescription medicines. Numerous patient surveys have highlighted that inhaled treatments are more likely to be used when asthma symptoms occur and avoided in the absence of symptoms.¹⁶⁸ Therefore, in 2019, GINA recommended as-needed low-dose ICS-formoterol in Step 1.¹ While this was initially an off-label recommendation, the publication of the SYGMA 1 and SYGMA 2 trials which compared budesonide/

formoterol with as-needed terbutaline or with regular budesonide plus as-needed terbutaline, provided firm evidence base for their recommendation.^{166,169} Both trials showed as-needed budesonide/formoterol was similar to budesonide maintenance at preventing severe exacerbations with substantial reduction in overall ICS dose (83% in SYGMA 1 and 75% in SYGMA 2). These results were replicated in the real-world Novel START study which confirmed non-inferiority of as-needed budesonide/formoterol compared to regular budesonide despite a 52% reduction in mean ICS dose.¹⁷⁰ However, maintenance budesonide was superior to as-needed budesonide-formoterol for asthma symptom control, measured by the Asthma Control questionnaire-5.

The other important advantage of as-needed low-dose ICS/LABA therapy in mild asthma is in the management of exacerbations. Patients on regular ICS or ICS plus LABA tend to rely on their SABA, which provides symptom relief but no anti-inflammatory effects. Replacing regular ICS with or without LABA with fast-acting LABA/ICS combination makes it possible to avoid SABA overuse and ensures that each time a patient takes an inhaler for symptom relief, they receive extra ICS. A recent meta-analysis has shown this approach results in a one-third reduction in risk of severe exacerbations.¹⁷¹

ICS/LABA as Maintenance and Reliever Therapy

It is well recognised that in the ~10 days preceding the commencement of oral steroids to treat an exacerbation, asthma symptoms and SABA use increases and this is usually accompanied by a decrease in peak expiratory flow (PEF).¹⁷² Symptomatic asthma is associated with worsening airway inflammation and therefore if an ICS is administered with the rescue bronchodilator, the patient would receive anti-inflammatory therapy when it is required, reducing symptoms and need for oral steroids. Indeed, the SMILE study in which patients with moderate to severe asthma treated with budesonide/formoterol as maintenance therapy received either SABA, formoterol or budesonide/formoterol to use as reliever therapy showed that the risk of severe exacerbation was reduced significantly with budesonide/formoterol maintenance and reliever.¹⁷³ Timely increase in ICS dose achieved by using ICS/LABA as maintenance and reliever therapy is more effective than higher doses of maintenance ICS/LABA and despite using the ICS/LABA as reliever therapy, the overall ICS use is lower than in fixed-dose regimes.^{174,175} While GINA has endorsed this for many years, the American NAEPPCC guidelines 2021 have finally recommended ICS/LABA maintenance and reliever therapy.^{1,44}

While there is firm consensus in all international guidelines on the role of ICS in all severities of asthma, the recent publication of the Steroids in Eosinophil Negative Asthma (SIENA) study adds some controversy.¹⁷⁶ Lazarus et al classified patients with mild asthma according to sputum eosinophil level (sputum eosinophil high $\geq 2\%$ or low if sputum eosinophil $< 2\%$). The patients were randomised to receive ICS, tiotropium or placebo with treatment response defined as a composite outcome that incorporated treatment failure, asthma control days and FEV₁. The

majority of patients (73%) were found to be sputum eosinophil low and there was no significant difference in their response to either ICS or tiotropium as compared to placebo. However, In the sputum eosinophil high group, ICS performed better than tiotropium.

In summary, all patients with asthma should receive inhaled steroid therapy, with low-dose as-needed ICS/LABA being a favourable option as it overcomes issues with poor adherence and cost-effective vs ICS and LABA as separate inhalers. We must move away from the historic distinction between so-called “intermittent” and “mild persistent” asthma as patients with few interval asthma symptoms can still have severe or fatal exacerbations.¹⁶⁰

Ultrafine-Particle Inhalers

Technological advances in device engineering and drug formulation have led to the development of inhalers emitting small-particle or ultrafine drug-aerosol which enhances drug deposition into the lung with more effective drug penetration into the lung periphery. This was driven largely by The Montreal Protocol of 1987 which required the eventual banning of all chlorofluorocarbons (CFC), including those in metered-dose inhalers (MDI).¹⁷⁷ Drug deposition into the lung periphery is particularly desired because airway inflammation in asthma affects the entire respiratory tract including the large, intermediate and small airways. Furthermore, many natural allergens, such as cat dander, fungal spores and pollen reach the distal airways^{178,179} and density of steroid receptors increases further down the airways.¹⁸⁰ Real-world studies show that treatment with small-particle aerosols resulted in better asthma control, improved quality of life and lower ICS dose compared with large particle aerosol treatment.¹⁸¹ These studies have led many to question why LABAs are added as a preferential step-up therapy when simply switching to an ultra-fine particle ICS could be attempted first. While this is an option, ICS/LABA combination inhalers are preferred for the reasons discussed above.

Montelukast

Cysteinyl Leukotrienes (CysLTs) are key mediators produced by airway immune cells and their interaction with the innate immune system leads to many of the pathogenic features of asthma including smooth muscle contraction, AHR, enhanced mucus secretion, increases vascular permeability, eosinophilic airway inflammation and airway remodelling.^{182,183} This recognition led to the development of CysLT receptor antagonists with

montelukast most widely used due its efficacy and safety profile. Leukotriene synthesis and CysLT receptor expression is not inhibited by steroids,^{184,185} further promoting the clinical utility of montelukast. Since its approval for use over two decades ago, montelukast has become established in stepwise asthma treatment algorithms. It is able to reduce SABA requirements, improve lung function, and reduce symptoms and risk of exacerbation in adults and children with asthma.^{186,187} However, more recently the clinical utility of montelukast in people with asthma and specific comorbidities is becoming increasingly recognised. These groups include people with asthma and rhinitis, exercise-induced asthma, asthma and obesity, aspirin-exacerbated respiratory disease, and preschool children with asthma and wheezing disorders.¹⁸⁸ In this era of precision medicine, the presence of these comorbidities should prompt clinicians to consider montelukast.

Azithromycin

Azithromycin is macrolide antibiotic that has antibacterial and anti-inflammatory effects. In a large randomised, double-blind, Australian study in moderate-to-severe asthma (AMAZES), azithromycin given three times a week reduced exacerbations (incidence rate ratio 0.59, 95% CI 0.47–0.74 compared to placebo) and improved asthma-related quality of life.¹⁸⁹ While it had been previously proposed that prophylactic macrolide therapy may be more beneficial in patients with non-eosinophilic sputum,¹⁹⁰ in this study, Gibson et al demonstrated that it reduced exacerbations in patients with eosinophilic as well as non-eosinophilic asthma. GINA recommends that it can be considered after specialist referral for adults with uncontrolled asthma despite high-dose ICS/LABA, but not used before a specialist review due to the potential risk of population-level antibiotic resistance.¹ In addition to reducing key inflammatory proteins (IL-6, IL1 β , extracellular DNA, tumour necrosis factor markers),^{191,192} azithromycin use is also associated with structural changes including increased airway lumen radius and area in patients with severe persistent asthma.¹⁹³ Airway abundance of *Haemophilus influenzae* has been shown to predict a more favourable response to azithromycin¹⁹⁴ and in our personalised approach to asthma management prospective assessment for the presence of *Haemophilus influenza* should be used to facilitate the identification of patients for this treatment.

Allergen-Specific Immunotherapy in Asthma

Allergen-specific immunotherapy (AIT) may be a treatment option when allergy is a prominent trigger for asthma symptoms and exacerbations. It can be delivered through two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The rationale behind and proposed mechanism for AIT is it modifies the underlying allergic pathways leading to allergen-specific tolerance and suppression of inflammation with clinical benefits seen in daily symptoms and exacerbations.¹⁹⁵ House dust mites (HDM) SLIT has been shown to delay time to exacerbation during ICS reduction in adults with suboptimally controlled asthma and HDM allergic rhinitis.¹⁹⁶ The European Academy of Allergy and Clinical Immunology recommends HDM-AIT as add-on treatment for HDM-driven allergic asthma as there is evidence it can reduce exacerbations and improve asthma control.¹⁹⁷ However, compared to pharmacological and avoidance options, the benefits of AIT need to be weighed against the cost to the patient and health system, potential side effects and inconvenience of the prolonged course of therapy.

Current Real-World Understanding of Biologics in Asthma

Multiple biologic drugs have entered clinical practice for severe asthma in recent years following an extensive portfolio of Phase 3 trials. A common approach of these monoclonal antibodies is precision management of T2 inflammation albeit by targeting different treatable traits. Here, we focus on emerging real-world data for five asthma biologics approved by the European Medicines Agency,^{198–202} namely Omalizumab, Mepolizumab, Reslizumab, Benralizumab and Dupilumab. Appreciating the real-world experience with such medication is increasingly important as real-life severe asthma patients often do not match the clinical trial populations in which these medications showed original efficacy.^{203,204} Findings are summarized in Table 3 and discussed in detail below.

Omalizumab

IgE plays a key role in mediating disease severity in allergic asthma. Allergen-specific IgE binds to the high-affinity receptor (Fc ϵ RI) on effector cells (mast cells, basophils) and antigen-presenting cells. Cross-linking of effector cell-bound IgE releases inflammatory mediators

Table 3 Current Biological Treatments in Severe Asthma. Targets, Eligibility, Dosing Regimen and Real World Impact

Biologic Name	Molecular Target	Eligibility Criteria for Adults (Based on EMA) ^{1–5}	Dosing Regimen	Real World Impacts
Omalizumab	Free IgE	As add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV ₁ <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.	2–4 weekly, subcutaneously based on Total IgE level and body weight	Improvement in FEV ₁ , Asthma control, exacerbations, OCS requirements, healthcare utilisation ^{26,211,221}
Mepolizumab	IL-5	Severe refractory eosinophilic asthma	100mg, 4 weekly, subcutaneously	Improvement in asthma control, exacerbations, OCS requirements, healthcare utilisation, AQLQ, FEV ₁ ^{26,117,239,241,275}
Reslizumab	IL-5	Severe eosinophilic asthma inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.	3mg/kg 4 weekly, intravenously over 20–50 minutes	Improvement in exacerbations, OCS requirements, FEV ₁ , healthcare utilisation ^{233,240}
Benralizumab	Alpha subunit of IL-5 receptor	As an add on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists.	30mg 4 weekly for the first three doses, then 8 weekly subcutaneously	Improvement in exacerbations, OCS requirements, healthcare utilisation, FEV ₁ , AQLQ ^{243–245,258}
Dupilumab	Alpha subunit of IL-4 receptor	Add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.	If on OCS + moderate-severe atopic eczema/CRSwNP: loading dose of 600mg followed by 300mg 2 weekly 400mg loading dose followed by 200mg 2 weekly, subcutaneously	Improvement in asthma control, exacerbations, FEV ₁ , OCS requirements ^{264–268}

Abbreviations: IgE, immunoglobulin E; FEV₁, forced expiratory volume in 1 second; OCS, oral corticosteroid; AQLQ, asthma quality of life questionnaire; ICS, inhaled corticosteroids; IgE, Immunoglobulin E; IL-5, Interleukin-5; IL-4, Interleukin-4.

with activation of downstream T-cell mediated allergic inflammation.²⁰⁵ Indeed, high specific IgE levels are associated with increased asthma healthcare utilization²⁰⁶ and asthma severity.²⁰⁷ Omalizumab was the first monoclonal antibody licensed for use in severe allergic asthma. It binds free IgE, thus preventing IgE binding to Fc ϵ RI on effector cells which are consequently down-regulated,²⁰⁸

and also inhibits CD23,²⁰⁸ a key player in antigen presentation. Over long term therapy, this drug also reduces IgE production,²⁰⁸ which may partly explain ongoing clinical efficacy with treatment cessation after long term use.²⁰⁹ Real-world studies have shown that the typical patients receiving Omalizumab are younger in age, have early-onset asthma, and had a higher reported history of co-

morbid atopic conditions such as allergic rhinitis.^{20,26} The multidimensional clinical efficacy of Omalizumab in such patients has been shown in meta-analyses of clinical trials.²¹⁰ Similarly, in meta-analyses of real-world observational studies, Omalizumab response rates are around 77%,²¹¹ with associated significantly improved exacerbation rate, FEV₁, oral corticosteroid use, and health care utilisation.^{211,212} Besides this, Omalizumab's real-world long-term safety profile is also well-established, with prospective studies suggesting no increased risk of side effects, such as anaphylaxis or malignancy.^{213–215} Importantly, a recent and ongoing prospective study (EXPECT) has also provided valuable insights into Omalizumab's safety in pregnancy. The investigators showed that the prevalence of major congenital defects, pre-term birth and other pregnancy-related adverse outcomes were not raised in Omalizumab treated pregnant women, compared to the general asthma population.²¹⁶ This may be useful to guide clinicians in biologic selection, in women planning pregnancy or who are pregnant, after careful consideration of risks and benefits, through joint decision making. Nonetheless, despite many years in clinical use, there is no agreement on factors predictive of Omalizumab treatment success. Post-hoc analyses of data from seven Omalizumab clinical trials found no baseline clinical characteristics reliably predicted Omalizumab efficacy.²¹⁷ Baseline circulating IgE levels have also shown little utility in this regard.²¹⁸ BEC, a surrogate marker of T2 status, displayed potential utility as a biomarker in post-hoc analyses of pivotal clinical trials,²¹⁹ and in the EXTRA study.²²⁰ However, large prospective and retrospective real-world studies found that patients responded equally well to Omalizumab regardless of their baseline BEC.^{221–223} A similar discordance between real-world and clinical trial data regarding the utility of FeNO in response prediction was also observed.^{220,221,223} Serum periostin, a marker of persistent T2 inflammation⁶¹ has shown potential as a stable and replicable biomarker of Omalizumab efficacy in both clinical trial²¹³ and real-world data.²²³ Indeed, post-hoc analysis of clinical trial data found that this biomarker had much lower intra-patient variability compared to measures such as FeNO.²²⁰ However, its utility may be limited by cost and it has yet to prove sufficiently compelling to cross over from an interesting research tool to mainstream clinical measure. Loss of efficacy or treatment failure inadvertently occurs in some Omalizumab treated patients. Interestingly, the severe eosinophilic and severe allergic

phenotypes are known to overlap.²²⁴ Indeed, we have previously shown that around 40% of Omalizumab treated patients potentially qualify for Mepolizumab, had it been available at the time.²⁶ Furthermore, there have been emerging real-world data on biologic switching from anti-IgE to anti-eosinophil agents^{225,226} in dual-eligible patients who did not respond to Omalizumab. This includes a real-world multicentre clinical trial (OSMO)²²⁷ where switching has shown to not only be safe, but also efficacious in improving asthma control, healthcare utilization and exacerbations, even without an Omalizumab washout period. Thus, in the current multiple biologics era, patients who have lost efficacy on Omalizumab should be worked up to be potentially switched to another class of biologic, such as anti-eosinophil treatments, depending on their biomarkers and other treatable traits.

Eosinophil-Targeting Biologics (Mepolizumab, Reslizumab and Benralizumab)

IL-5 is a key mediator in eosinophilic inflammation in asthma through enabling eosinophil survival, differentiation, maturation, migration and proliferation.²²⁸ Raised IL-5 has been shown to correlate with asthma severity.²²⁹ Additionally, it has also been shown to be implicated in airway remodelling in both murine and human models.²³⁰ In recent years, there has been an influx of monoclonal antibody therapies targeting this cytokine, licensed for patients who exhibit eosinophilia alongside meeting nation-specific severity criteria commonly defined by oral corticosteroid dependency. Such biologics include Mepolizumab^{231,232} and Reslizumab,^{233,234} which target circulating IL-5 itself, while Benralizumab targets the alpha subunit of the IL-5 receptor (IL-5R).^{235–237} These biologics are eosinophil depleting and have been not only efficacious but also safe in clinical trials, whereby the common side effects (headache, injection site reactions, back pain, pharyngitis) were mostly mild-moderate.^{231–237} Real-world studies have similarly shown that these drugs were safe and efficacious, with response rates around 70%, and improvements in clinical asthma outcomes (exacerbations, OCS dependence, asthma control, quality of life, lung function), as early as 4-weeks into therapy.^{26,238–248} Their clinical efficacy was also observed in real-world patients who had failed Omalizumab therapy.^{225,226,249,250} Real-world characterisation of patients receiving anti-IL-5/IL-5R drugs has identified

a group who are older in age, have adult-onset asthma, predominantly male and have a high prevalence of nasal polyposis.^{20,26} Nonetheless, not all patients respond well to these drugs, despite careful patient selection. Notably, most real-world studies of the different anti-IL5 agents have found that those with a more severe baseline disease, measured in terms such as Asthma control questionnaire-6, were less likely to respond and “super-respond” to these drugs.^{26,239,241} This is understandable as patients with more severe, difficult asthma likely have multiple treatable traits beyond eosinophilic inflammation driving their poor symptom control.^{26,251} In such circumstances, switching between biologics within the same pathway may be useful. Indeed, several retrospective reports have shown that the switch from Mepolizumab non-responders to Benralizumab resulted in improvements in exacerbations, OCS dose and asthma control.^{242,251} Similar trends were also demonstrated for switching Mepolizumab to Reslizumab in a small single-blinded placebo-controlled trial.²⁵² Nonetheless, despite these emerging signals, the source of such observations have small sample sizes. Thus, more robust, prospective data is required to help inform in-class switching. Such data is also needed to inform the safety of these agents in the context of pregnancy, given that there are only a few case reports of such use across the three agents to date.^{253,254} Regarding biomarkers, post-hoc analyses of clinical trial data have suggested that baseline BEC may potentially be the most useful predictor of treatment response to these agents.^{56,255–257} This was also observed in real-world settings,^{239,258} but not consistently.^{26,238,259,260} A large, real-world Australian registry of Mepolizumab found that those with high BEC are more likely to respond.²³⁹ Similarly, Kavanagh et al found higher baseline BEC predicted “super-response” in their UK, Benralizumab treated patients.²⁵⁸ However, they also showed BEC was not useful in predicting Mepolizumab response.²⁵⁸ Two multi-centre studies from Italy^{238,246} and another real-world UK study²⁶ similarly did not find BEC useful in predicting treatment response. This discrepancy may reflect different patient groups or the limited utility of cross-sectional eosinophil evaluation.²² It could also be that in a subset of patients, IL-5 may not be the main determinant of their eosinophil-mediated disease.²⁶¹ In these patients, perhaps targeting other T2 cytokines such as IL-4 and IL-13, which are often co-expressed with IL-5, may be preferable.

Dupilumab

Dupilumab is a humanized monoclonal antibody directed against the alpha subunit of the IL4 receptor, which

antagonizes both IL-4 and IL-13.^{48,262,263} These mediators induce key features of T2 driven allergic asthma such as goblet cell metaplasia, IgE production and bronchial hyperresponsiveness.⁷ Blockade of such mechanisms translates to improved clinical outcomes, as evidenced by this drug’s efficacy in clinical trials.^{48,261–263} Additionally, post-hoc analyses of the QUEST clinical trial data found it was efficacious even in those without allergic asthma.²⁶⁴ Given its relatively recent and to date selective worldwide approval, limited real-world data is available for this drug. One of these was a multi-centre retrospective analysis on²⁵⁶ unselected, severe asthma patients in France.²⁶⁵ These patients were at a therapeutic dead-end and prescribed Dupilumab on a nominative Authorization for Temporary Use basis. The authors found that the efficacy of Dupilumab in this real-world cohort was comparable to clinical trials, whereby this drug improved asthma control, exacerbations and medication requirements.²⁶⁵ Other reports similarly provide evidence for the aforementioned multidimensional real-world efficacy of Dupilumab.^{266–268} Even more crucially, in a real-life setting, this drug was efficacious in those who had failed treatment with other asthma biologics.^{265,267,268} Indeed, in a recent retrospective study, patients who had an insufficient response to anti-IL-5/IL-5R or anti-IgE biologics, who were then switched to Dupilumab, showed improvements in asthma control, exacerbations and OCS requirements.²⁶⁹ This again suggests that inadequate response to a specific biologic should not be accepted as implying poor response to other biologics. No definitively useful predictors of treatment response were found in these studies, including baseline BEC. This corroborates but also contrasts findings from clinical trials. A pivotal phase 2b trial,²⁶³ and the phase 3 trials QUEST⁴⁸ and VENTURE²⁶² study evidenced Dupilumab efficacy, regardless of the levels of this biomarker. However, these studies found more robust improvements in those with high BEC^{48,262,263} and FeNO.^{48,262} Regardless, while the evidence of the efficacy of this drug in real-world settings is emerging, more data is required to identify biomarkers of treatment response to Dupilumab, to aid patient selection. Additionally, while this drug has shown a good safety profile in clinical trials, whereby adverse effects were again mild-moderate (viral upper respiratory tract infection, eosinophilia, sinusitis, injection site reactions)²⁰² there are yet no real-world, asthma-specific data on the long-term safety and efficacy of this drug. Similarly, while there are case reports and case series of the use of this drug in treating atopic

dermatitis during pregnancy,^{270–272} there are none for asthma. In these regards, the ongoing Global Dupilumab registry (RAPID)²⁷³ may help fill this need.

Monoclonal Antibody Selection for Asthma and Comorbidities

Monoclonal antibody therapies are finding increased use in comorbid T2 conditions encountered alongside asthma. Dupilumab is currently licensed by the EMA for the treatment of moderate to severe atopic dermatitis and severe chronic rhinosinusitis with nasal polyps (CRSwNP).²⁰² It also has a specific license from the EMA, for patients with severe T2 asthma who have co-existent severe eczema or CRSwNP.²⁰² Similarly, anti-IL-5 and IL-5R drugs, following successful clinical trials, are also currently under assessment for approval by multiple regulatory bodies for use in other eosinophilic conditions such as Eosinophilic Granulomatosis with Polyangiitis,^{248,274} CRSwNP^{275–277} and Eosinophilic oesophagitis.²⁷⁸ Mepolizumab specifically has been approved by the Food and Drug Administration for Eosinophilic Granulomatosis with Polyangiitis²⁷⁸ Finally, Omalizumab is also licensed for use in treatment-resistant chronic spontaneous urticaria and CRSwNP.¹⁹⁸ The emergence of biologic use in these

other disease states may conceivably inform asthma biologic choice in the future as shown in Figure 2. It also once again highlights the importance of a holistic “whole-person” approach to phenotyping, by looking beyond asthma and considering comorbid treatable traits in biologic selection.

Future Treatments

Currently, licenced biologic treatments target downstream pathways of T2-inflammation and reduce exacerbation rates in study populations by approximately only 50%. Furthermore, there are limited treatment options for the seemingly few patients with T2-low severe asthma. With improved understanding of the immunopathogenesis of asthma, additional therapeutic targets within inflammatory pathways are being explored.

Recently published data show the effectiveness of Tezepelumab, a biologic that targets upstream T2-inflammation, in patients with severe, uncontrolled asthma.²⁷⁹ Tezepelumab blocks thymic stromal lymphopoietin (TSLP)- an epithelial-cell-derived alarmin central to the regulation of T2-immunity. TSLP acts on numerous immune cells inducing the production of T2-cytokines, ultimately resulting in airway eosinophilia, AHR and

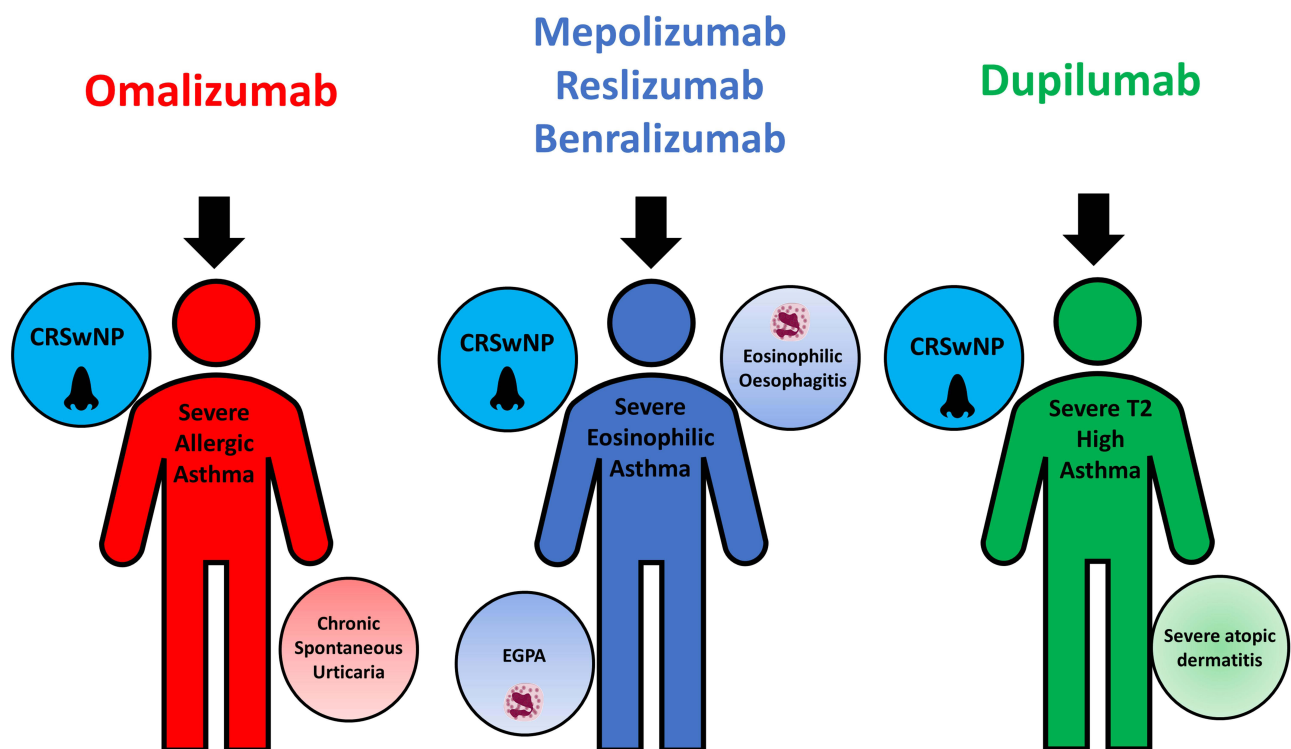


Figure 2 Biologic drugs in severe asthma and treatable traits potentially amenable to treatment by them.

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, Eosinophilic Granulomatosis with Polyangiitis.

airway remodelling.^{280–282} In NAVIGATOR, a phase 3 trial, patients who received Tezepelumab had significantly fewer exacerbations and better lung function, asthma control and health-related quality of life, regardless of BEC, although the benefits were greater in patients with BEC \geq 300 cells/ μ L.

Fevipirant is an oral, highly selective, reversible antagonist of the prostaglandin D2 receptor (DP2). This receptor is expressed on key inflammatory cells including eosinophils, airway smooth muscle and epithelial cells. While Phase II studies in patients with asthma showed fevipirant reduced sputum eosinophilia, improved lung function, as well as symptoms and quality of life, this efficacy was not replicated in a worldwide Phase 3 clinical trial programme.²⁸³ Nevertheless, there may be patient subgroups that benefit from fevipirant and future studies are awaited.

Dexramipexole is a novel oral eosinophil lowering drug which in a phase 2 study has been shown to significantly reduce BEC in patients with moderate-to-severe asthma.²⁸⁴ The reduction in BEC was dose-dependent and seen alongside improvement in FEV₁. It is thought to deplete eosinophils by inhibiting their maturation in the bone marrow, without affecting mature eosinophils. The drug is going to be studied as a potential pre-biologic alternative in the UK BEAT Severe Asthma Consortium Trials Program.

Conclusion

Asthma is a heterogeneous disease hallmarked by T2-inflammatory pathways. Anti-inflammatory treatments are the mainstay of asthma treatment and ICS are now recommended for all patients with asthma. While conventional asthma treatments are broadly effective, recognising other treatable traits and using biomarkers to identify underlying inflammatory phenotypes helps to personalise treatment and improve asthma control. Monoclonal antibody treatments represent a new treatment era in severe asthma for patients who are uncontrolled despite high-dose anti-inflammatory treatment. However, currently available biologics fail to prevent all exacerbations, highlighting once again the importance of treating other treatable traits and the need to continue to explore inflammatory pathways for novel therapeutic targets.

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