

Beyond T2-inflammation: What Does the Future Hold for Severe Asthma?

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ABSTRACT

Asthma is a common inflammatory airways disease affecting over 300 million people. It is considered severe in 5-10% of cases, with poor disease control despite a high burden of treatment. Severe asthma encompasses a heterogeneous pathobiology reflecting host-environment interactions at all scales of disease from the genetic to organ level. Characterisation of the T2-endotype has led to significant reductions in exacerbations for patients with eosinophilic disease, however control is incomplete in some, likely due to contributing factors that may include poor adherence to current therapy and co-existence of distinct pathological processes within the individual. In this article we consider where attention should be directed in the future in severe asthma; strategies to improve the use of current licensed therapies, therapeutic targets beyond T2 inflammation, and how expectations should adapt to reflect progress in managing disease overall. (BRN Rev. 2019;5(2):74-89)

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INTRODUCTION

Asthma affects over 300 million people worldwide¹, amongst whom severe asthma describes a heterogeneous group of 5-10% with disease that either remains uncontrolled despite treatment with systemic corticosteroids (ICS) and/or high dose inhaled corticosteroids or requires these therapies to prevent loss of control². Severe asthma is characterised by frequent exacerbations and significant symptoms with increased risk of treatment-associated morbidity especially in response to exposure to systemic corticosteroids³. Severe asthma represents about half of the total economic burden of the disease⁴.

Severe asthma is a heterogeneous condition. This heterogeneity in asthma pathogenesis is well recognised⁵ and clinical presentation reflects complex interactions between host and environmental factors at all scales of disease, from the genetic to organ level (Fig. 1). As understanding of disease mechanisms improves throughout these levels through a 'systems medicine' approach, identification of key drivers has allowed development of new therapies.

Often, but not always, associated with allergy, the most common asthma endotype is T2 immunity high, with a characteristic cytokine profile of interleukin (IL)4, IL5 and IL13 contributing to eosinophilic inflammation. This has been the focus of recent therapy development. Non-T2 inflammation asthma is less well understood and represents an unmet clinical need, as patients are often poorly responsive to current therapies⁶. Neutrophilic inflammation with activation of T1/T17 pathways may be present, along with other disease drivers including airway remodelling, airway hyper-responsiveness

(AHR), oxidative stress and recurrent infection. It is recognised that environmental factors have a significant impact on disease (the exposome) although at present, the majority of these factors have been studied in isolation and further study is required to determine the host response to multiple exposures that occur sequentially and in parallel across time.

In this article we evaluate severe asthma according to current management paradigms, highlight the success in targeting type 2 immunity-mediated biologics and consider where the future lies for severe asthma, including: how we can optimise current management strategies, novel approaches to treatment particularly focusing on management beyond T2 inflammation and how expectations should be adapted to reflect progress in managing the disease overall.

SEVERE ASTHMA: WHERE ARE WE NOW WITH CURRENT THERAPIES?

Severe asthma is defined in those for whom 'guidelines suggested medication for Global Initiative for Asthma (GINA) steps 4-5 asthma (high dose ICS and long-acting β_2 -agonists [LABA] or leukotriene receptor antagonist [LTRA]/theophylline) or regular oral corticosteroids are required for $\geq 50\%$ of the previous year to prevent it becoming uncontrolled or which remains uncontrolled despite this therapy'². Poor control is defined as ongoing symptoms, frequent or serious exacerbations or reduced measures of lung physiology.

As suggested, evidence-based therapies for severe asthma include high dose ICS and LABA. Evidence for LTRAs and theophylline is less robust but these may be beneficial in some and

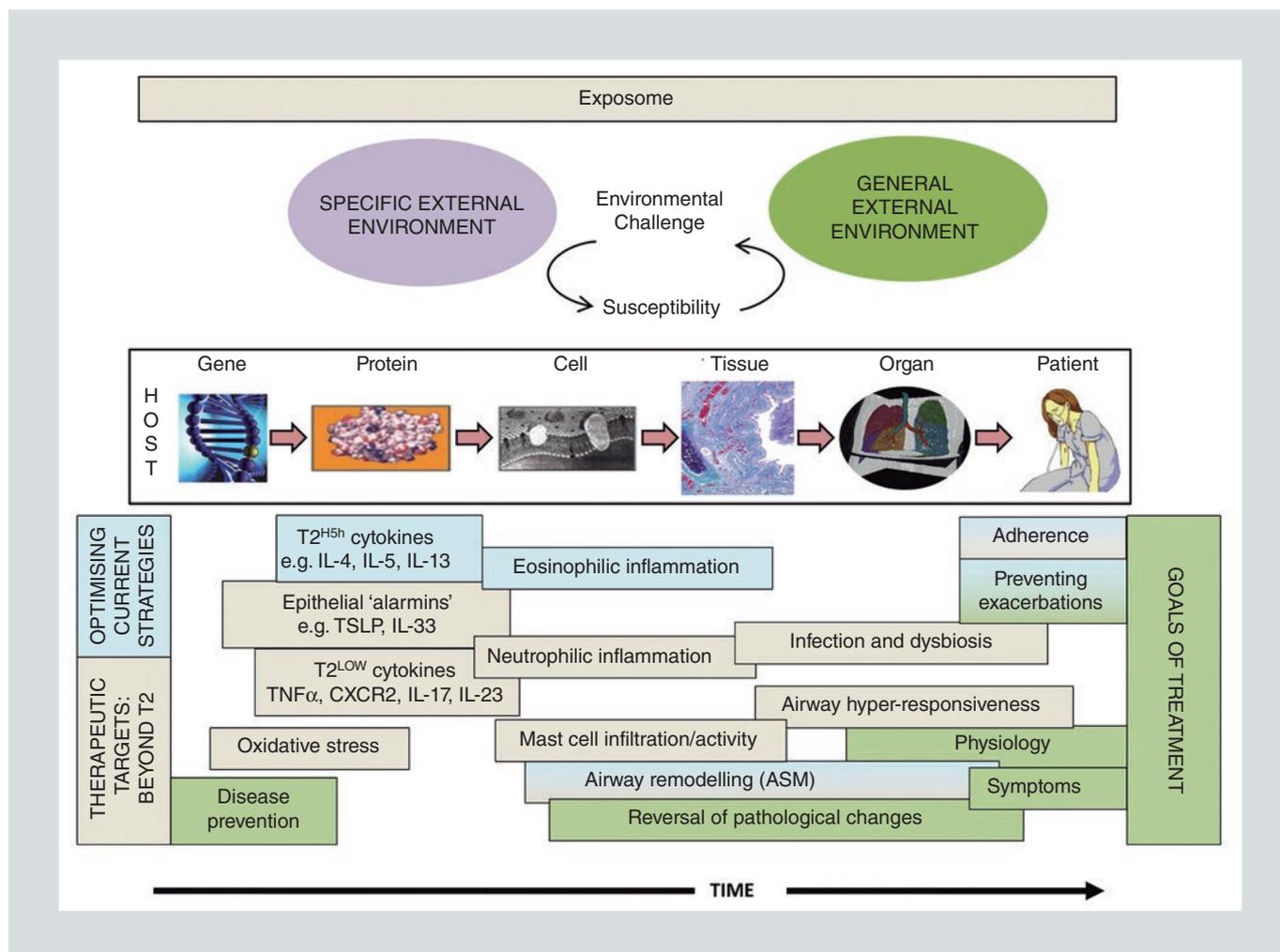


FIGURE 1. Considering the future of severe asthma at incrementing scales of disease, including optimisation of current strategies, therapeutic targets beyond T2 inflammation and goals of treatment.

ASM: airway smooth muscle; CXCR2: CXC chemokine receptor-2; IL: interleukin; TNF- α : tumour necrosis factor- α ; TSLP: thymic stromal lymphopoietin.

are associated with less long-term morbidity than alternatives such as oral corticosteroids². Addition of long-acting anti-muscarinic (LAMA) bronchodilators in severe asthma led to improvement in forced expiratory volume in one second (FEV₁) and increased time to first exacerbation, especially in the subgroup with greater airflow obstruction at baseline⁷.

Whilst maintenance systemic corticosteroids are often instigated for uncontrolled severe

asthma, there are no randomised controlled trials (RCTs) demonstrating benefit, despite a wide recognition of the unfavourable risk profile of treatment³. Using biomarkers to direct treatment can improve efficacy⁸, and this strategy is recommended in international guidelines².

Current licensed therapies and interventions in severe asthma are listed in table 1. The focus in asthma drug development has targeted

TABLE 1. Phase 3 trials of current licensed therapies and interventions for severe asthma

Specific agent/intervention	Population	Outcomes
Anti-IL5 (R)		
Mepolizumab 100 mg SC Q4W for 24 weeks Chupp 2017 ⁸⁴	N = 556, Adults/children > 12 years Blood eosinophils $\geq 300/\mu\text{l}$ in last 12 months or $\geq 150/\mu\text{l}$ at screening, ≥ 2 exacerbations in last year FEV_1 : < 80% adults, $\leq 90\%$ 12-17 years	SGRQ: \downarrow 7.7 points versus placebo Exacerbations: \downarrow 42% FEV_1 : \uparrow 20ml
Mepolizumab 100 mg SC Q4W for 20 weeks Bel 2014 ⁹⁵	N = 135, Age 16-74 Blood eosinophils $\geq 300/\mu\text{l}$ in last 12 months or $\geq 150/\mu\text{l}$ at screening 5-35mg maintenance prednisolone (or equivalent) for > 6 months	Oral corticosteroid use: \downarrow ~50% Exacerbations: \downarrow 32% ACQ: \downarrow ~0.52
Mepolizumab 100 mg SC Q4W or 75 mg IV Q4W for 32 weeks Ortega 2014 ⁸⁶ , Ortega 2016 ⁸⁷	N = 576 Adults/children > 12 years Blood eosinophils $\geq 300/\mu\text{l}$ in last 12 months or $\geq 150/\mu\text{l}$ at screening	Exacerbations: \downarrow ~50% FEV_1 : \uparrow 100ml, ACQ: \downarrow ~0.43 \downarrow exacerbations 70% where blood eosinophils $\geq 500/\mu\text{l}$
Reslizumab 3 mg/kg IV Q4W for 16 weeks Corren 2016 ⁸⁸	N = 492 Age 12-65 $> 12\%$ bronchodilator response	FEV_1 : no significant change Eosinophil ^{HIGH} FEV_1 : \uparrow 270 ml, ACQ: 0.49
Reslizumab 0.3 mg/kg IV Q4W or 3 mg/kg IV Q4W for 16 weeks Bjerner 2016 ⁸⁹	N = 315 Age 12-75 Blood eosinophils $\geq 400/\mu\text{l}$ ACQ ≥ 1.5	3mg/kg dosing FEV_1 : \uparrow 160ml ACQ: \downarrow 0.36 AQLQ: \uparrow 0.36
Reslizumab 3 mg/kg IV Q4W for 52 weeks Castro 2015 ⁹⁰	N = 953 (study 1 = 489, study 2 = 464), Age 12-75 Blood eosinophils $\geq 400/\mu\text{l}$ ≥ 1 exacerbation in last year, ACQ ≥ 1.5 , $> 12\%$ bronchodilator response	Exacerbations: \downarrow 54% FEV_1 : \uparrow 110ml ACQ: \downarrow 0.25, AQLQ: \uparrow 0.23
Benralizumab 30 mg SC Q4W or 30 mg SC Q8W for 28 weeks Nair 2017 ⁹¹	N = 953 (study 1 = 489, study 2 = 464), Age 12-75 Blood eosinophils $\geq 400/\mu\text{l}$ ≥ 1 exacerbation in last year, ACQ ≥ 1.5 , $> 12\%$ bronchodilator response	Exacerbations: \downarrow 54% FEV_1 : \uparrow 110 ml ACQ: \downarrow 0.25, AQLQ: \uparrow 0.23
Benralizumab 30 mg SC Q4W or 30 mg SC Q8W for 28 weeks Nair 2017 ⁹¹	N = 220, Age 18-75 Blood eosinophils $\geq 150/\mu\text{l}$ at screening 7.5-40 mg maintenance prednisolone (or equivalent) for > 6 months	Oral corticosteroid use: \downarrow ~75% Exacerbations: \downarrow 55-70%
Benralizumab 30 mg SC Q4W or Q8W for 48 weeks Bleecker 2016 ⁹² , Goldman 2017 ⁹³	N = 1205 Age 12-75 ≥ 2 exacerbations in last year ACQ ≥ 1.5 FEV_1 : < 80% adults, $\leq 90\%$ children $> 12\%$ bronchodilator response	Eosinophil ^{HIGH} Exacerbations: \downarrow ~50% FEV_1 : \uparrow 100-150ml ACQ: \downarrow ~0.25, AQLQ: \uparrow ~0.25 \downarrow exacerbations ~40% where blood eosinophils $\geq 150/\mu\text{l}$
Benralizumab 30 mg SC Q4W or Q8W for 56 weeks Fitzgerald 2016 ⁹⁴ , Fitzgerald 2018 ⁹⁵	N = 306 As above	Eosinophil ^{HIGH} Exacerbations: \downarrow ~30% FEV_1 : \uparrow 120ml ACQ: \downarrow ~0.2, AQLQ: \uparrow 0.2 Greater \downarrow in exacerbations with \uparrow blood eosinophils and \uparrow frequency of exacerbations pre-treatment
Anti-IL4Rα		
Dupilumab 200 mg SC Q2W or 300 mg SC Q2W for 52 weeks Castro 2018 ⁹⁶	N = 1902 Adults/children > 12 years ≥ 1 exacerbation in last year ACQ ≥ 1.5 FEV_1 : < 80% adults, $\leq 90\%$ 12-17 years $\geq 12\%$ and 200 ml bronchodilator response	Exacerbations: \downarrow ~50% FEV_1 : \uparrow 320-340ml ACQ: \downarrow ~0.3 AQLQ: \uparrow ~0.3 \downarrow exacerbations 65% where blood eosinophils $\geq 300/\mu\text{l}$ and FeNO > 25 ppb

(continued)

TABLE 1. Phase 3 trials of current licensed therapies and interventions for severe asthma (*continuation*)

Specific agent/intervention	Population	Outcomes
Dupilumab 300 mg SC Q2W for 24 weeks Rabe 2018 ⁹⁷	N = 210, Adults/children >12 years 5-35 mg maintenance prednisolone (or equivalent) for > 6 months FEV ₁ : < 80% adults, ≤ 90% 12-17 years ≥ 12% and 200 ml bronchodilator response	Oral corticosteroid use: ↓ ~70% Exacerbations: ↓ 59% FEV ₁ : ↑ 220ml
Bronchial thermoplasty		
3 treatments 3 weeks apart with follow-up to 52 weeks Castro 2010 ¹⁹ , Wechsler 2013 ²⁰	N=288, Age 18-65 AQLQ ≤ 6.25 FEV ₁ : ≤ 60%, PC20 < 8 mg/ml, ≥ 2 days of symptoms during 4-week baseline period	AQLQ: ↑ 0.19 Exacerbations: ↓ severe exacerbations 32% Follow up to 5 years: ↓ exacerbations 44%, ↓ ED visits 78%

ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; ED: emergency department; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in one second; IL: interleukin; SC: subcutaneous; SGRQ: St. George's respiratory questionnaire.

type 2 immunity mediated inflammation⁹⁻¹¹, the most common inflammatory phenotype¹²⁻¹³, with three biologic drug classes available to clinicians which significantly reduce exacerbations in severe asthma through action against immunoglobulin E (IgE)¹⁴, IL5 or the IL5 receptor¹⁵, and most recently IL4Rα¹⁶. Further to these, other agents, both biologics and small molecules, have demonstrated success in early phase trials. In particular, phase 2 trials of the anti-thymic stromal lymphopoietin (TSLP) agent, tezepelumab, at low, medium and high dosing demonstrated a 60-70% reduction in exacerbations in subjects with eosinophils ≥ 250 per µL, whilst > 70% reductions were observed across dosing groups in those with fractional exhaled nitric oxide (FeNO) ≥ 24ppb¹⁷. In a phase 2a trial, the oral prostaglandin D₂ receptor 2 (DP2) antagonist, fevipiprant, improved symptom control, quality of life and lung function measures compared to placebo over 12 weeks in asthmatics with sputum eosinophilia¹⁸, with results of phase 3 trials awaited.

In addition to these T2-mediated therapies, bronchial thermoplasty (BT) is a licensed therapy for severe asthma. It involves pulsed application of radiofrequency energy to the airway wall bronchoscopically inserted via a catheter. The complete procedure requires three treatment sessions separated by three-four week intervals, with clinical trials demonstrating fewer exacerbations and hospitalisations maintained at up to five years of follow-up^{19,20}. A recent evidence review suggests that although there is a degree of uncertainty in predicting those who will respond positively, BT should be considered in severe asthma, under the supervision of a specialist multi-disciplinary team²¹. Whilst the positive impacts reported following BT are thought to relate to reduction in airway smooth muscle (ASM) as a direct response to heat, biopsy studies have shown an improvement in epithelial integrity post-BT, and have used mathematical modelling to demonstrate that other mechanisms may contribute to ASM reduction²² suggesting that further study at a mechanistic level is indicated.

SEVERE ASTHMA: WHERE ARE WE GOING?

I. Optimising current treatment strategies

Introduction of adjunctive therapies for uncontrolled asthma, which may represent both a substantial impact on patients' daily routine and a significant cost to healthcare systems, must be considered only after adequate evaluation of adherence to current treatment, which has been frequently demonstrated to be poor, with non-adherence reported in over 50%²³. Current strategies to improve adherence include patient self-report, analysis of prescription refills, dose counting or weighing of inhaler canisters and measurement of drug levels, although all these methods potentially lack accuracy²⁴. The electronic monitoring device INhaler Compliance Assessment (INCA™) was used in combination with a 7-day period of daily FeNO monitoring (the FeNO Suppression Test) in difficult-to-control, severe asthmatics with FeNO > 45ppb. Positive FeNO suppression test (as defined by a reduction in FeNO of $\geq 42\%$), in the setting of appropriate inhaler use, prior to one month of monitoring was associated with significant improvements in lung function that were not observed in those who did not suppress their FeNO, although both groups demonstrated improvement in symptom scores²⁵, and these results suggest that there may be benefit to implementing systematic adherence assessments in the clinical setting. "Smart inhalers" with the ability to objectively monitor and prompt inhaler use present an opportunity to improve outcomes in asthma, and the potential benefits have been recognised by bodies such as Asthma UK²⁷ although challenges

would be faced in effectively implementing this technology into healthcare systems.

As above, it is recognised that biomarker-directed therapy can improve treatment efficacy². In addition to proven biomarkers such as sputum eosinophils⁸, it is clear that valuable information regarding underlying disease mechanisms and future exacerbation risk in individuals can be obtained through measurement of blood eosinophils and FeNO. Further trials are in progress to ascertain whether combining these more widely accessible biomarkers of T2 inflammation can safely and appropriately facilitate corticosteroid titration²⁷. Other potential markers include measurement of volatile organic compounds in exhaled breath for use in asthma diagnosis and differentiation between disease phenotypes²⁸. Using biomarkers specific to independent disease processes can help to identify where these are active and coexist within individual patients. Using this "systems health" approach "treatable traits"^{29,30} emerge and their identification can be a useful tool for clinicians to personalise therapy profiles.

Whilst biomarkers can help us to identify those likely to benefit from additional treatment, with multiple therapeutic options demonstrating efficacy over placebo, randomised head-to-head trials directly comparing biologics and other interventions in severe asthma, alone and in combination, are required to inform clinical decision making in future. For example, the phase 4 Study of magnitude and prediction of response to omalizumab and mepolizumab in adult severe asthma (Predictumab) (NCT03476109)³¹ randomises subjects to omalizumab versus mepolizumab

in those eligible for both treatments, and aims to not only compare effectiveness, but identify clinical and biological markers predictive of response. Subjects who fail to demonstrate a response to their initial treatment will crossover to receive the other drug, allowing investigators to analyse differences in response within the individual. Further pragmatic trials supported by national and international respiratory societies, on a scale allowing adequate generalisability, comparing other interventions in severe asthma will also be required³².

II. Beyond T2 inflammation: mechanisms and potential therapies

T2 low inflammation. Compared to T2 high eosinophilic inflammation, T2 low inflammation is less well characterised. Typically, it is associated with late onset, non-atopic disease, poorly responsive to corticosteroids⁶. Inflammation can be neutrophilic in response to increased CXC chemokine receptor 1/2 (CXCR1/2) chemokines such as C-X-C Motif Chemokine Ligand 8 (CXCL8). T1/T17 pathways have been implicated in T2 low disease but these are not fully defined³³. Pathways may be common upstream of differentiation to T2 high and T2 low mediated inflammation, therefore targeting the epithelial “alarmins”; TSLP, IL33 and IL25 may lead to improvements across both endotypes⁵.

A number of therapies targeting T2-low inflammation have been trialled although with limited success. Tumour necrosis factor (TNF)- α inhibitors have been successful in a number of systemic inflammatory conditions and were

initially promising, although the mechanism of action in asthma was debated³⁴. Later phase trials did not demonstrate a clear benefit and, worryingly, found increased frequency of cancer and pneumonia³⁵. A trial of anti-CXCR2 failed to demonstrate an effect over placebo on asthma exacerbations, symptom scores or physiology despite reducing blood neutrophil counts³⁶. The anti-IL17 agent, brodalumab, failed to impact on asthma control or lung function across moderate-to-severe asthma³⁷. A follow-up study in subjects with high bronchodilator reversibility was terminated at interim analysis due to lack of effect³⁸. Trials of anti-IL23 in severe asthma have been discontinued.

As discussed above, the anti-TSLP agent tezepelumab has demonstrated improvements in exacerbation rates and lung function, which is promisingly independent of T2 inflammation¹⁷, with a reduction in exacerbation rate > 50% across dosing groups in asthmatics with blood eosinophils < 250 cells/ μ L. Unpublished data from phase 2a studies of an anti-IL33 agent suggesting positive impacts on physiology however included only subjects with baseline eosinophilia³⁹.

Airway remodelling describes a number of modifications in airway structure including; epithelial thickening or loss of integrity, ASM muscle hyperplasia and hypertrophy, subepithelial fibrosis, mucous gland and goblet cell hyperplasia, and neoangiogenesis⁴⁰, and can occur in both child and adult asthma, indicating an independent disease mechanism rather than a consequence of chronic inflammation⁴¹. Increased ASM predicts airflow obstruction and, with epithelial thickness, is associated with reduced luminal area on

quantitative computed tomography, whilst airway vascularity predicts gas trapping⁴².

Several therapeutic strategies have been suggested to target remodelling in asthma, including BT which has already been discussed. Drug therapies targeting smooth muscle include the calcium-channel blocker, Gallopamil, which was evaluated in a 12-month, double-blind, placebo-controlled, proof of concept trial⁴³. Whilst a reduction in bronchial smooth muscle mass was observed in the treatment group, this was not significantly different from the change in structure observed in the control group. Promisingly, a post-hoc analysis of biopsies from patients receiving the oral anti-DP2 agent, fevipiprant, over 12 weeks has demonstrated that this treatment was able to reduce ASM, employing a computational modelling approach to suggest that this effect could not be solely attributable to effect on eosinophilic inflammation⁴⁴. Effects on ASM were not demonstrated with mepolizumab⁴⁵, however these results support the need for high quality mechanistic studies characterising the impact of new biologics on remodelling, as this may highlight potential benefits in other subgroups of patients.

Airway hyperresponsiveness reflects airway narrowing in response to direct or indirect stimuli and is a consequence of augmented ASM contractility, occurring independently of inflammatory phenotype. Mast cells are co-located to the ASM bundle. Through production of cytokines they promote ASM survival, activation and contractility, and their number are associated with the degree of AHR^{40,46,47}. High-mobility group box 1 (HMGB1) has been shown to be upregulated in severe asthma⁴⁸, and potentiates ASM contraction via toll-like

receptor 4, which may lead to ASM dysfunction and AHR through a reduced capacity to generate reactive oxygen species (ROS). Whether this represents a potential therapeutic target requires further study. Animal studies have demonstrated that Metallothionein-2 (MT-2) can relax ASM and reduce pulmonary resistance via transgelin-2 (TG2)⁴⁹. In vitro, treatment of human ASM cells with the specific TG2 agonist, TSG12, reduced resistance more effectively than β_2 -agonists and may represent a further target for smooth muscle dysfunction in asthma.

Clinical trials targeting AHR in asthma include inhibition of mast cell development and survival through the KIT proto-oncogene receptor tyrosine kinase inhibitor, imatinib⁵⁰. 62 patients were randomised in the double blind, placebo-controlled trial which evaluated the impact of 24 weeks of treatment on airway reactivity. Imatinib increased the methacholine PC₂₀ by 1.73 ± 0.60 doubling doses, which was significantly greater than increases demonstrated in the control group over the course of the trial.

Oxidative stress reflects biological damage occurring due to the presence of excessive reactive oxygen and nitrogen species (ROS and RNS) relative to protective antioxidants. At present, the aetiological role of oxidative stress in asthma remains unclear. Quantification of oxidative stress directly is difficult, however extensive work has characterised indirect biomarkers of oxidative stress including those representing the effects of ROS on proteins, lipids and DNA (Fig. 2). In the Unbiased BIOMarkers in Prediction of REspiratory Disease outcomes (U-BIOPRED) severe asthma cohort, systemic oxidative stress was found to be increased

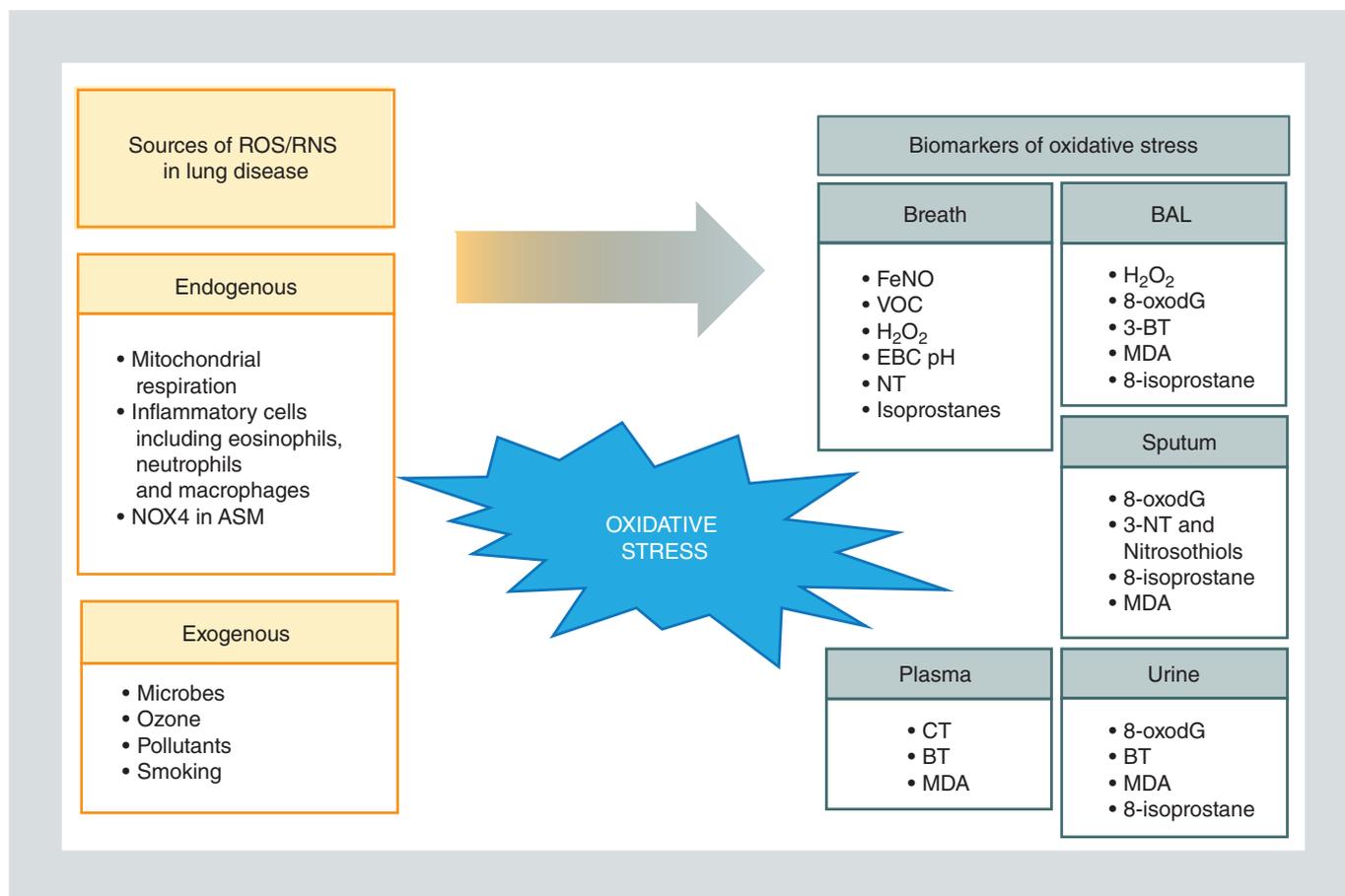


FIGURE 2. Endogenous and exogenous sources of reactive oxygen and nitrogen species in the lung, and measurable biomarkers of oxidative stress caused by these according to compartment.

3-BT: 3-bromotyrosine; 3-NT: 3-nitrotyrosine; 8-oxodG: 8-hydroxyl-2'-deoxyguanosine; ASM: airway smooth muscle; BAL: bronchoalveolar lavage; BT: bronchial thermoplasty; CT = chlorotyrosine; EBC pH: pH of exhaled breath condensate; FeNO: fractional exhaled nitric oxide; H₂O₂: hydrogen peroxide; MDA: malondialdehyde; NOX4: nicotinamide adenine dinucleotide phosphate oxidase 4; NT: nitrotyrosine; RNS: reactive nitrogen species; ROS: reactive oxygen species; VOC: volatile organic compounds.

in smokers compared to ex- or never smokers⁵¹. Measurement of 8-oxodG levels in a real-world asthma population showed that high levels of systemic oxidative stress were associated with airway neutrophilia and high airway bacterial load, and that future exacerbation risk was lowest in those with combined low oxidative stress and bacterial burdens⁵². Further characterisation of the role of oxidative stress in asthma pathogenesis is required to ascertain whether potential

treatments should target environmental triggers, for example smoking cessation and antimicrobials for airway infection, or whether directly targeting downstream mechanisms, for example, through antioxidants will lead to greater success.

Exposome. An overarching concept to consider is the exposome, which refers to the cumulative exposures that a patient is subjected to over their lifetime, encompassing; the general

external environment (e.g., air pollution), the specific internal environment (e.g., smoking or physical activity), and the impact of this internal environment on the individual as measured by omic tools⁵³. Omics platforms have already been used to demonstrate, for example, that air pollution impacts on the genome, epigenome, transcriptome and metabolome in asthma, or that specific genetic polymorphisms will influence a child's risk of developing asthma following viral infection⁵⁴. Other exposures already demonstrated to be associated with severe asthma are listed in table 2. At present, these exposures have been studied in isolation, and it is likely that omics platforms will be integral to define the combined effects of multiple exposures occurring across time within individual patients. Biomarker development is key, and will include measurement of markers of exposure, markers of susceptibility and markers of disease or response to individual triggers (Fig. 3).

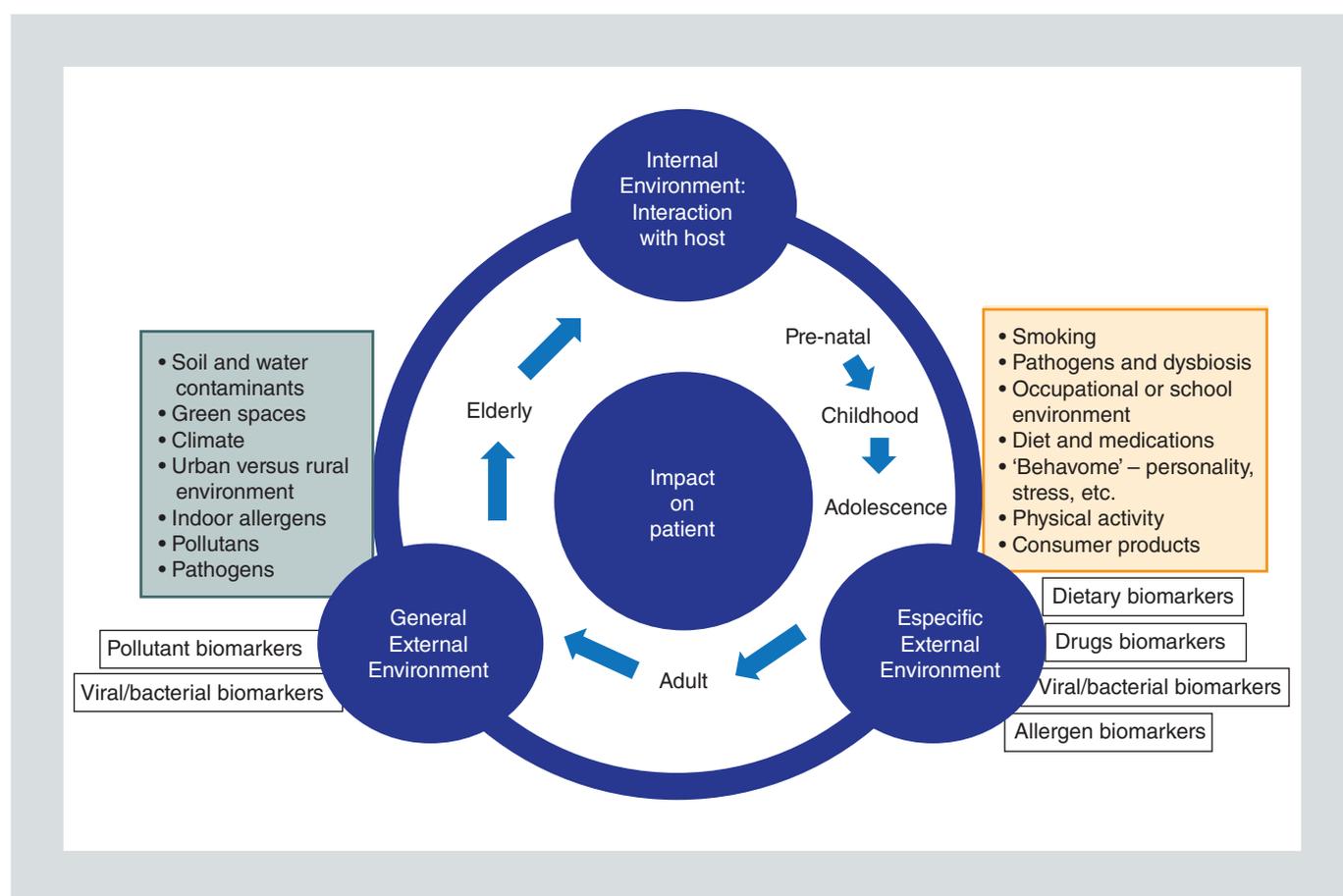
Understanding the complex interactions between host and environment will require respiratory communities to collaborate, to integrate layers of exposomic data, with development of bioinformatics platforms that allow interrogation of large datasets. It is not yet clear whether the exposome is best addressed at a population or individual level however public health interventions to reduce exposures on a large scale clearly have the potential to impact on disease management. Measurement of environmental exposures chronologically presents an opportunity to understand how these contribute to development of disease, which may lead to interventions that can prevent disease. The Human Early Life eXposome (HELIX)⁵⁵ is

an initiative including six European birth cohorts that has compared both pre- and post-natal exposures to multiple omics profiles to better characterise the exposome over time.

Dysbiosis and infection. Environmental pathogens are a component of the exposome and it is well recognised that bacteria, viruses and fungi may impact on disease course in severe asthma. Subgroups with bacterial disease drivers during clinical stability and at exacerbation may be distinct from subgroups with other biological drivers^{56,57}, which may be related to predominance of key pathogens, such as Proteobacteria^{58,59} and, more specifically, *Haemophilus influenzae*, within the microbiome⁶⁰. Evidence for the use of macrolide antibiotics is unclear. Initial trials suggested a benefit in non-eosinophilic but not eosinophilic asthma⁶¹ but a recent large RCT has demonstrated benefit across moderate-to-severe asthma in reducing moderate and severe exacerbations, independent of inflammatory phenotype⁶². Subgroup analysis of this trial did, however, report greatest benefit in those with positive bacterial culture. An increase in treatment-resistant organisms was documented over the trial period and macrolide use in severe asthma in future will need to be weighed against the potential public health risks of rising antibiotic resistance. Identification of specific bacterial pathogens will allow strategies other than broad-spectrum antibiotics to be considered. Augmenting *Haemophilus*-specific immunity through use of an adjuvanted vaccination to non-typeable *H. Influenzae* has been trialled in chronic obstructive pulmonary disease (COPD), although the impact of this on clinical outcomes is not yet

TABLE 2. Environmental factors associated with severe asthma, including those described and currently under study

	General external environment	Specific external environment
Adults	Air pollution ⁹⁸	Occupation ⁹⁹ Smoking ¹⁰⁰ Obesity ¹⁰¹ Aspirin sensitivity ¹⁰² Medication adherence ¹⁰³ Environmental fungi including <i>Aspergillus</i> ^{72,104} Airway microbial profile e.g., <i>C. pneumoniae</i> ^{56,105}
Children	Air pollution ¹⁰⁶	Low socioeconomic status ¹⁰⁷ Obesity ¹⁰⁸ Allergen exposure ^{109,110} Tobacco smoke exposure ¹¹¹

**FIGURE 3.** The Exposome: Environmental exposures, and biomarkers of these exposures, comprising the general and specific external environment which may impact in severe asthma over a patient's lifetime.

reported⁶³. Phage therapy reduced bacterial load and inflammatory responses in mice infected with *P. Aeuruginosa* in a model of acute lung infection, and has potential to allow

targeting of specific pathogens⁶⁴. The gut-lung axis is a well-established concept in microbiome research⁶⁵, and another less specific approach would be to target the respiratory

microbiome indirectly via an intervention directed at the gastrointestinal (GI) tract. The impact of probiotic therapy on disease control in mild-moderate asthma will be evaluated through planned clinical trials⁶⁶. Staphylococcal enterotoxins with superantigen activity are raised in severe asthma compared to non-severe asthma⁶⁷, which may represent a therapeutic target.

Viral infection, particularly rhinovirus, is a well-recognised aetiological factor in asthma exacerbations and is associated with suboptimal interferon responses^{68,69}. Although a trial of inhaled interferon- β did not improve asthma control questionnaire (ACQ)-6 scores across severities in asthmatics with acquired viral infection, analysis of those with moderate-to-severe disease demonstrated a significant improvement compared to placebo⁷⁰. Levels of serum CXCL10 were augmented as were genes for antiviral biomarkers in sputum, indicating enhanced innate immunity. Based on previous work demonstrating the association with cell surface IgE in dendritic cells with reduced interferon responses, a 4-month targeted treatment strategy employing omalizumab for at-risk inner-city asthmatic youths reported a reduction in seasonal exacerbations compared to placebo in those on step 5 treatment, with the subgroup who experienced an exacerbation during the run-in period demonstrating an 88% reduction in exacerbations over the 3-month outcome period⁷¹. Fungal sensitisation is present in up to 50% of those with severe asthma⁷², however, to date, anti-fungal treatment in subjects with severe asthma not meeting criteria for Allergic Bronchopulmonary Aspergillosis (ABPA) has not been efficacious in reducing severe exacerbations or improving quality of life⁷³. Trials of inhaled

triazole therapy⁷⁴ and anti-interleukin 1 receptor-like 1 (ILRL1)⁷⁵ in fungal asthma remain ongoing.

III. Shifting paradigms in acute and chronic severe asthma

Whilst recent T2-directed agents have achieved success in reducing asthma exacerbations and improving lung function and health status, these remain components of, rather than total, asthma control and will be more or less important at the individual patient level. Recent therapies have had little impact on symptoms and evidence suggests that exacerbations are dissociated from symptoms and physiology⁶. Symptoms may be caused by unrelated pathology with alternative therapeutic targets, such as fixed airflow obstruction. Evaluation of how these outcomes can be targeted may lead to changes in the goals of treatment. Significant improvements in asthma symptoms may not be achieved without reversal of pathology such as airway remodelling, leading to a shift in focus on to disease remission or cure. Current therapies have not proven efficacy for this, although agents in development have indicated promise⁴⁴.

Positioning of new therapies in early disease, including in children, will help us to understand their role in onset and early progression, whilst characterising the exposome and defining the relationships between exposures and individual susceptibility also indicates potential for disease prevention. A recent genome wide association study, including 10,549 cases of moderate-to-severe asthma, identified a number of genes associated with type 2 inflammation and remodelling, and, interestingly,

showed that the majority of genetic signals overlap in severe and mild disease, suggesting that epigenetic and environmental factors are fundamental to disease progression⁷⁶. Defining how these factors in concert with the exposome lead onto the onset of asthma and therefore highlighting strategies for prevention will be important in the future. Determining how to prevent mild-to-moderate asthma becoming severe will be a major focus of new therapies which in themselves might redefine the classification of severe asthma itself.

In addition to treatment of chronic asthma, treatment of acute asthma will need to be re-evaluated in the context of new therapies. At present, approach to exacerbation management does not include phenotypic differentiation⁷⁷, however analysis of exacerbation episodes in airways disease patients suggests this could be important to delivering appropriate treatment⁵⁶. Measurement of biomarkers indicating microbial aetiology will be important, such as Proteobacteria:Firmicutes (P:F) ratio for bacterial exacerbations, which has been evaluated in both asthma and COPD^{56,78}. For eosinophilic exacerbations, strategies such as increasing the dose of ICS four-fold at the onset of exacerbation symptoms reduced the need for systemic corticosteroids by 19%⁷⁹ in a population of mixed severities. Exacerbations may also present an opportunity to commence biologic therapy in selected patients, with one study of the anti-IL5R antibody, benralizumab, delivered in the emergency department reducing asthma-related hospitalisations over the 12-week follow-up period⁸⁰. As described above, a significant number of exacerbations are viral in aetiology, and trials suggest that antiviral therapy such as inhaled interferon- β could improve immunity⁷⁰. Regarding bacterial

events, a study of telithromycin⁸¹ demonstrated an improvement in symptom scores in an unselected population of asthmatics with an acute exacerbation, however the drug was later withdrawn due to concerns over safety profile. A follow up study of azithromycin failed to show benefit but was underpowered due to widespread antibiotic use pre-hospital limiting recruitment⁸². At present, antibiotics for acute asthma are not recommended⁸³, but better differentiation of exacerbation events is needed to identify those most likely to benefit.

CONCLUSIONS

Progress of biologic therapies directed against T2 inflammation through clinical trials into practice has allowed improvement in control of severe asthma for many patients, alongside reduction of corticosteroid dose and the positive impact of reduced exposure to comorbidities associated with this treatment. We have considered the future of severe asthma in the context of these agents.

Regarding available biologic agents, key questions remain to be addressed after regulatory approval. With the aim of total control in mind, biological responses of complete, partial and non-responders, with respective biomarkers, need to be considered to understand how further treatment can be delivered. Equally, where patients are eligible for multiple therapies, head-to-head randomised pragmatic trials are required to guide first-line and subsequent management³².

Where poor control exists despite treatment this may be due to comorbidity, suboptimal adherence or pathological processes beyond

T2 inflammation. Promising results of agents targeting epithelial ‘alarmins’ suggest that targeting upstream inflammation may positively impact both T2 and non-T2 inflammation, with phase 3 trials of anti-TSLP eagerly awaited. The reduction in ASM observed with fevipiprant, in excess of anti-inflammatory effects alone⁴⁴, indicates that disease remission for those with airway remodelling is a realistic prospect, and supports the implementation of mechanistic trials for new agents to characterise their effects at a histological level.

Expectations will then need to be raised further to include cure and disease prevention³². These will represent significant challenges, however international collaborations following subjects and their environmental exposures through the pre-natal period, childhood and further will provide a wealth of data that will aid our understanding of why disease develops, and may indicate where intervention could prevent this.

DISCLOSURES

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