

REVIEW ARTICLE



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Different endotypes and phenotypes drive the heterogeneity in severe asthma

P. Jane McDowell | Liam G. Heaney

Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK

Correspondence

Liam G. Heaney, Centre for Experimental Medicine, Wellcome-Wolfson Institute for Experimental Medicine, 97 Lisburn Road, Belfast BT9 7BL, UK.
Email: l.heaney@qub.ac.uk

Abstract

The identification of sputum eosinophilia indicating corticosteroid responsiveness in subjects with severe asthma heralded the beginning of phenotyping asthmatic subjects based on airways inflammation. Since then, the heterogeneity of severe asthma has been explored and the importance of immunobiology has come sharply into focus with the identification of the key type-2 cytokine pathways driving eosinophilic inflammation. The development of molecules targeting these type-2 pathways has transformed severe asthma treatment, but necessitates robust clinical evaluation, biomarker profiling and assessment of comorbid factors to identify subjects most likely to benefit from these therapies. It has also become clear that targeting these pathways does not eradicate asthma symptoms and exacerbation risk; further work is needed to clarify underlying non-type-2 mechanisms in severe asthma pathways and possible therapeutic targets. This review addresses progress to date in clinical assessment and management of severe asthma and some of the challenges and unmet needs in severe asthma to achieve the goal of delivering individualized patient care.

KEYWORDS

adherence, biomarkers, endotype, phenotype, psychosocial factors and severe asthma

1 | INTRODUCTION

In 1958, Dr Harry Morrow Brown published a seminal paper in the *Lancet*, which demonstrated the clinical response to corticosteroids in patients with chronic persistent asthma was associated with the presence of eosinophils in sputum.¹ This study was performed after the United Kingdom Medical Research Council subcommittee on clinical trials in asthma reported no advantage of cortisone acetate in the treatment of chronic asthma, which was a result that many including Dr Morrow Brown found surprising.² This outcome may have been due in part to the study design and reported outcomes but also in part to the inclusion of a heterogeneous patient population with a clinical diagnosis of asthma. Many years later, a study using

sputum samples induced with hypertonic saline also demonstrated that patients with asthma and a sputum eosinophil count $\geq 3\%$ had a greater response to inhaled corticosteroids (ICS) compared to those with an eosinophil count $< 3\%$.³ Woodruff and colleagues subsequently demonstrated that an IL-13-derived epithelial gene signature (periostin, serpin B2 and CCLA1) was associated with airway eosinophilia and upregulation of type-2 cytokines IL-5 and IL-13 but importantly this gene signature was only seen in 50% of asthmatics who had withdrawn ICS.⁴ Further, reintroduction of ICS was again associated with an improvement in lung function in subjects with evidence of eosinophilia and upregulation of type-2 cytokines, but which importantly was not seen in those subjects without evidence of airway type-2 inflammation/eosinophilia. The authors coined the terms Th2-high and Th2-low asthma and reinvigorated the debate about noneosinophilic asthma and, importantly, asthma which is not responsive to ICS. In another study, using data from the National Asthma Research Programme in the United States, McGrath and

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colleagues also demonstrated that subjects with mild-to-moderate asthma and no evidence of sputum eosinophilia (defined as sputum eosinophil count <2%) had no improvement in lung function with ICS but showed evidence of a bronchodilator response consistent with asthma.⁵ This study also identified that in ICS naive subjects, 47% have no evidence of sputum eosinophilia in serial samples taken at various points over a 1-year period but this proportion increased to 72% in subjects currently taking ICS treatment. Taken together, these data would suggest that substantial groups of patients with mild and moderate asthma have little evidence of type-2 cytokine-driven airway eosinophilia (T2-low asthma) and by extension are likely to have little response to either initiation or escalation ICS treatment.

McGrath and colleagues also reported that the patients with noneosinophilic mild asthma had less bronchial hyperresponsiveness than those with airways eosinophilia. Likewise, Arron and colleagues demonstrated an inverse relationship between an IL13-high gene signature (T2-high asthma) and bronchial hyperresponsiveness, suggesting that T2-low/noneosinophilic disease is associated with less physiological abnormality.^{5,6} This is supported by data which suggest that noneosinophilic asthma is associated with lower risk of asthma exacerbation and there is strong evidence that surrogate biomarkers of type-2 airways inflammation (blood eosinophil count, fractional exhaled nitric oxide [FeNO], serum ECP and serum periostin) are all prognostic biomarkers for exacerbation.⁷⁻⁹ The evidence is most robust for elevated blood eosinophil count and FeNO, which have consistently been associated with a higher exacerbation rate in the placebo arms of clinical trials in patients with severe asthma selected on the basis of a prestipulated biomarker threshold.¹⁰⁻¹² Taken together, this would suggest there are those with persistent symptoms who meet the diagnostic criteria for severe asthma (Box 1)¹³ but have little evidence of active T2-driven disease. Although these patients are biomarker low and have a

Major Milestone Discoveries

- Characterisation of type-2 cytokine pathways, which have allowed identification of molecular targets for biological therapies.
- Development of novel biological therapies effective in treating type-2 cytokine-driven eosinophilic severe asthma.
- Identification of clinically useful biomarkers of type-2 inflammation that are easily measured, are prognostic for exacerbation, aid phenotyping and guide treatment in severe asthma.
- Development of smart inhalers with aligned biomarker profiling to define treatment pathways in severe asthma.

Future Research Perspectives

- A greater understanding of non-type-2 mechanisms driving asthma to enable the development of biomarkers and identification of therapeutic targets.
- Clarity around the factors and mechanisms driving residual severe exacerbations in type-2 high asthma treated with biologics targeting these pathways.
- Further data on molecules targeting epithelial alarmins in the treatment of severe asthma.
- Elucidating the best interventions to improve adherence in subjects with severe asthma likely to benefit from regular treatment with inhaled corticosteroids.
- Identification and development of disease-modifying treatments for severe asthma.

Box 1 GINA guideline definitions of uncontrolled asthma, difficult-to-treat asthma and severe asthma¹³

Uncontrolled asthma

Defined as one or both of the following:

- Poor symptom control
- Frequent exacerbations

Difficult-to-treat asthma

Defined as either of the following:

- Uncontrolled asthma despite GINA 4/5 treatment
- Asthma that requires GINA 4/5 treatment to maintain good control and reduce exacerbation risk

Severe asthma

Defined as either of the following:

- Asthma uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors
- Asthma that worsens when high-dose treatment is decreased

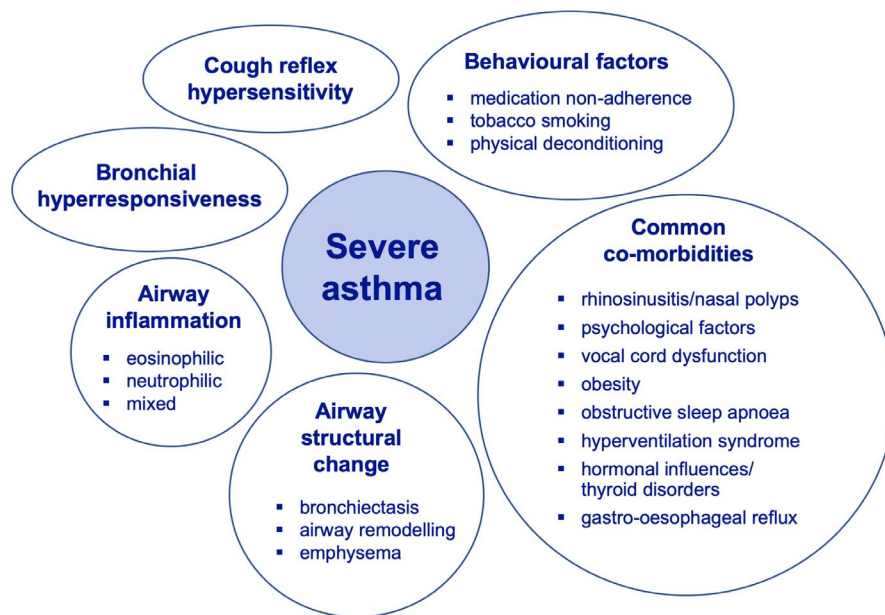


FIGURE 1 Deconstructing severe asthma into component parts which can be identified and potentially addressed in the clinic—this includes extra-pulmonary factors that can contribute to persistent symptoms (reproduced with permission from reference¹⁷). These factors may evolve with time, necessitating regular patient evaluation¹³

comparatively low exacerbation risk, it is important to comment that severe asthma exacerbations still occur in these symptom high, type-2 biomarker-low patients albeit at a much lower rate.

It is recognized that treatment with corticosteroids will down-regulate type-2 inflammation and related biomarkers and that prednisolone may have a larger effect on peripheral blood eosinophil count compared with sputum eosinophil count or FeNO.¹⁴⁻¹⁶ High-dose ICS and oral corticosteroid therapy are therefore an important confounder in subjects with more severe asthma. This raises two important issues—firstly, whether true T2-low asthma exists in more severe asthma when corticosteroids are down titrated and secondly, what is the mechanism of persistent symptoms in subjects with asthma when type-2 corticosteroid-responsive asthma is not present. As discussed above, “true” T2-low asthma appears to be relatively common in mild asthmatic subjects who do not require regular ICS treatment but is generally associated with mild symptoms, less bronchial hyperresponsiveness and a lower risk of asthma exacerbation compared to subjects with T2-high disease. Intuitively, it seems improbable that this group of patients would be progressed to high-dose ICS treatment; however, if symptoms are persistent and not ICS responsive as appears to be the case, it is possible that some of these patients may be escalated to high-intensity treatment to try and improve their symptoms. The issue of whether true T2-low asthma exists in severe asthma is currently being explored in the RASP-UK programme, where patients are having corticosteroids “downtitrated” if their biomarkers of T2-driven disease are low.¹⁷ This study offers much needed exploration of the use of T2 biomarkers in high-dose ICS and oral corticosteroid-treated asthmatics, and a comparison of their performance to more traditional markers such as sputum eosinophil counts. The other question on the mechanism of persistent symptoms and lung function impairment in T2-low asthma (type-2 biomarker-low patients) is discussed further below.

2 | DISEASE STRATIFICATION IN SEVERE ASTHMA—UNRAVELLING COMPLEXITY

The 2018 GINA Guideline on difficult-to-treat and severe asthma in adults and adolescents outlines the definitions for uncontrolled, difficult-to-treat and severe asthma (Box 1).¹³ It is recognized that severe asthma is a complex clinical problem which is not exclusively about airways inflammation and response to treatment—behavioural factors, common comorbidities, cough reflex hypersensitivity, bronchial hyperresponsiveness and structural change are all features that may be related or separate to inflammatory events in the airways (Figure 1).¹⁸ Over a decade ago, studies of severe asthma cohorts first described the contribution of multiple comorbidities to patients' disease burden.^{19,20} These comorbidities appear to be very reproducibly represented in severe asthma cohorts and where possible should be considered potential targets for intervention or “treatable traits” in severe asthma.^{21,22} As an exemplar of this complexity and how important it is to have a holistic approach to the assessment of poorly controlled severe asthma, Ten Brinke and colleagues examined risk factors for frequent exacerbations in difficult-to-treat asthma and demonstrated psychological dysfunction was the greatest driver of recurrent exacerbation in this population.²³ Thus, detailed systematic assessment, including a firm diagnosis of asthma and identification of all contributing factors and particularly traits which are potentially treatable, is an important part of clinical assessment in severe asthma rather than continually escalating treatment in response to persistent symptoms.²⁴

3 | FAILURE TO RESPOND TO INHALED CORTICOSTEROID TREATMENT

Assuming a robust diagnosis of asthma and that other factors contributing to symptoms have been identified and addressed insofar as

is possible, there are broadly speaking three reasons why patients with asthma do not respond to ICS treatment in the clinic⁷:

1. Nonadherence: ICS responsive but not taking ICS treatment.
2. Relative resistance to corticosteroids: Persistent type-2 inflammation despite good adherence with high-dose ICS treatment (before biological therapy, these patients usually progressed to maintain systemic steroids).
3. Non-T2 mechanisms: ICS unresponsive mechanisms.

In terms of inhaled medication nonadherence, this is known to be common and remains the major challenge in achieving much better asthma control. Adherence with inhaled treatment in mild asthma can be less than 35% of prescribed treatment when compared to objective monitoring.^{25,26} Even in UK patients with severe asthma who were very prone to exacerbation and had a high symptom burden, 65% of new referrals for specialist assessment collected less than 80% of their inhaled preventive medication.^{27,28} In an elegant study from the Netherlands, 17.4% of the adult asthma population had "difficult-to-control" asthma (poor asthma control despite prescription of high-intensity treatment) but after excluding nonadherence/poor inhaler technique, only 3.6% had severe refractory asthma.²⁹

Nonadherence is consistently associated with poor clinical outcomes including death, hospital admission, poor control and quality of life.³⁰⁻³² It is economically expensive for healthcare systems due to increased healthcare utilization costs, systemic corticosteroid-induced morbidity in severe disease³³⁻³⁵ and the potential for inappropriate escalation of treatment to the novel biological therapies targeting the type-2 cytokine axis. In mild asthma, recent data have suggested that as required use of a combination inhaled rapid onset long-acting β_2 -agonist and ICS inhaler may be a good option for treating mild disease.^{36,37} This strategy is superior to as required short-acting β_2 -agonist alone and equivalent to regular ICS (with good adherence) in terms of exacerbation reduction, but regular ICS treatment appeared to deliver overall better asthma control. As anticipated, the exacerbation rate in this mild population is relatively low so an as required treatment strategy in patients with intermittent symptoms may be intuitively more attractive and deliverable in the mild asthma population.

However, there are patients with more severe asthma where as required ICS treatment is unlikely to be effective and where regular treatment needs to be delivered to maintain disease control and reduce exacerbation risk. As a starting point, it is helpful in this population to confirm that type-2 inflammation is present and the use of easily measureable biomarkers of type-2 inflammation such as FeNO and blood eosinophil count should be advocated prior to "blindly" escalating treatment in this population. FeNO is an excellent biomarker of response to ICS,^{15,38} and it has previously been shown that suppression of this biomarker with 5 days of directly observed treatment is useful to identify nonadherence in subjects referred for specialist assessment with poor asthma control despite prescription of GINA 4/5 treatment.³⁹ This type

of approach facilitates the identification of patients who would achieve a good response to better adherence with inhaled treatment but also identifies patients who, despite adequate treatment with high-dose ICS treatment, are likely to have persisting type-2 inflammation and will probably require escalation to novel biologic therapies.³⁸ The advent of novel "Smart inhalers" aligned with biomarker profiling (FeNO and blood eosinophil count) will make this an important process in the clinic prior to treatment escalation.^{40,41} It is important to note alignment of ICS exposure using a "smart inhaler" technology with biological response is a "phenotyping" process to identify where to initiate novel biologic treatments but also to identify those patients to target adherence interventions. It does not "fix" poor adherence but relatively simple interventions, such as mobile text messaging in chronic disease management, have been shown to improve adherence and simple reminder systems have also been shown to improve inhaled maintenance treatment in asthma.^{42,43} The pharmaceutical industry is now moving into smart inhaler technology with digitally connected inhaler systems; however, we need further studies to define the best intervention to improve adherence in subjects where optimized inhaled treatment is likely to be effective.

4 | RECENT NOVEL THERAPEUTIC ADVANCES

Novel treatments in severe asthma target components of the type-2 cytokine axis (Figure 2). In a recent Cochrane review of 13 studies examining add-on mepolizumab, reslizumab and benralizumab in *ca* 6000 patients with poorly controlled, severe eosinophilic asthma (either ≥ 2 exacerbations in preceding year/ACQ ≥ 1.5) despite standard treatment, all reduced exacerbation rates (rescue OCS ≥ 3 days) by approximately 50%.⁴⁴ There were modest improvements in symptoms and asthma-related quality of life measured by ACQ and AQLQ (which did not meet the minimally clinically important difference [MCID]) with improvements in St. George's Respiratory Questionnaire (SGRQ) assessed in two studies. A small improvement in prebronchodilator FEV₁ of 80-110 mL was noted. There were no excess serious adverse events with anti-IL-5 treatment, although drug discontinuation was significantly more for benralizumab than placebo; however, the numbers were small (36/1599 benralizumab versus 9/998 placebo). Benralizumab and mepolizumab have also been shown to reduce oral corticosteroid dose compared to placebo with a parallel reduction in exacerbation rate.^{45,46} Drugs targeting IL-13 alone (lebrikizumab and tralokinumab) have demonstrated less efficacy than anticipated in phase 3.^{47,48} However, dupilumab, which targets the IL4 receptor preventing IL-4 and IL-13 signalling, demonstrated a significant reduction in severe exacerbations (47.7% reduction for 200 mg dupilumab compared to placebo, $P < 0.001$) and additionally demonstrated lung function improvement which was evident early after treatment initiation (at week 12, FEV₁ increased 0.14 litres compared to placebo, $P < 0.001$).¹¹ Dupilumab treatment also resulted in a significant reduction in OCS in subjects on maintaining OCS treatment (70.1%

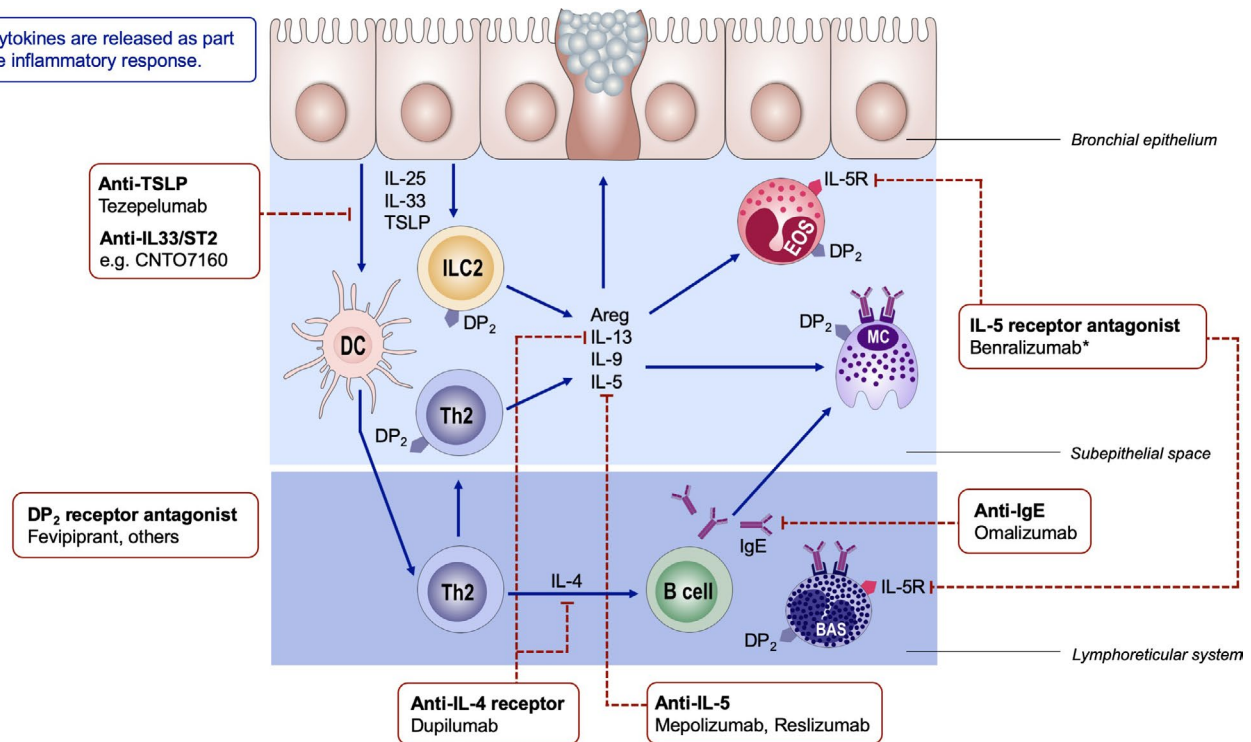


FIGURE 2 Novel therapies in severe asthma target components of the type-2 cytokine axis. anti-IL4R, anti-IL4 receptor antagonist; anti-IL5R, anti-IL5 receptor antagonist; DC, dendritic cell; DP2, prostaglandin D2 receptor; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type-2; PGD2, prostaglandin D2; EOS, eosinophil; MC, mast cell; BAS, basophil

with dupilumab vs 41.9% in the placebo group [$P < 0.001$] with a 59% lower exacerbation rate than placebo and mean increase in FEV1 of 0.22 litres more than placebo).⁴⁹

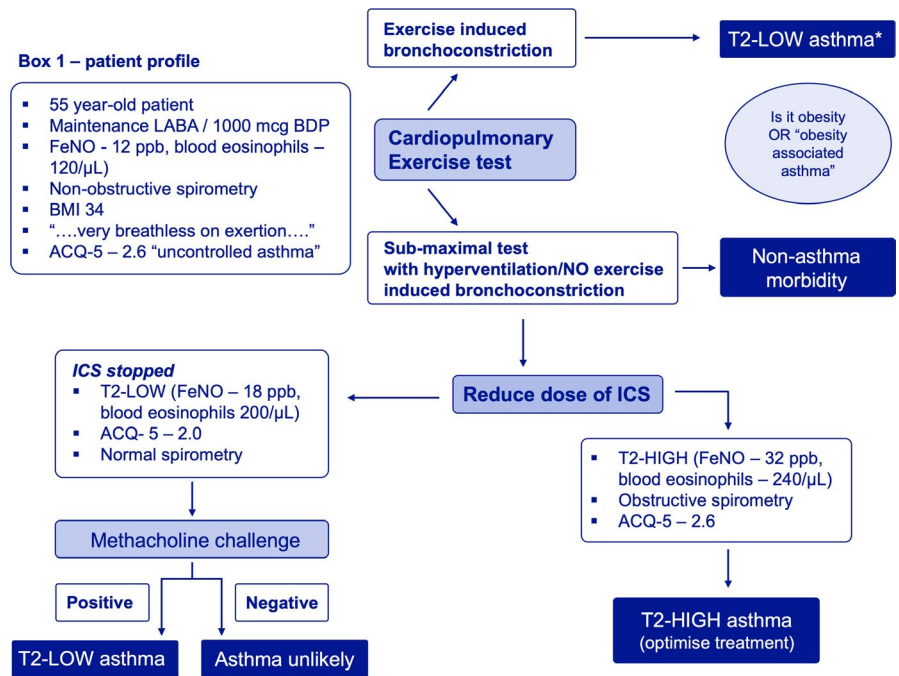
In all these studies, it has become clear that type-2 biomarkers (FeNO and blood eosinophils) are not only prognostic for severe exacerbations, they are also predictive of therapeutic response to these therapies. In other words, for anti-IL5 treatment, in patients with a higher peripheral blood eosinophil count, there is a greater therapeutic effect.^{50–54} Similarly for dupilumab, a greater treatment effect is seen in patients with either increased FeNO or peripheral blood eosinophil count.¹¹ The current evidence on the role of T2 biomarkers as a predictor of response to anti-IgE therapy is conflicting. Post hoc analysis of pivotal clinical trials reported a greater reduction in exacerbations with omalizumab treatment in T2 biomarker-high subgroups.^{55,56} In contrast, real-world observational studies STELLAIR and PROSPERO have shown no difference in exacerbation reduction between the biomarker-high and biomarker-low subgroups treated with omalizumab.^{57,58} What may also be clinically useful is that these studies have helped identify biomarker thresholds for blood eosinophil count and FeNO, where intervention with a drug targeting the type-2 cytokine axis is unlikely to deliver significant clinical benefit—specifically little benefit is seen if blood eosinophil count is <150 cells/ μL (anti-IL-5/anti-IL-4R) and FeNO is <25 ppb (anti-IL-4R).^{43,49} It has become clear that the available type-2 biologics target overlapping clinical populations, and it remains to be seen if these biomarkers can also be helpful in selecting the best drug for individual patients. For example in a patient who has a blood eosinophil count <150 cells/ μL

but elevated FeNO, then dupilumab may be a better therapeutic option, but this remains to be tested in clinical trials or potentially in real-world clinical settings using severe asthma clinical registries. A 50% reduction in severe exacerbations has been seen consistently in clinical trials targeting the IL-5 or IL4/13 axes, and understanding the mechanism of the residual severe exacerbations with these therapeutic interventions is a pressing unmet need in severe asthma.

Tezepelumab targets thymic stromal lymphopoietin which is an epithelial alarmin and in a phase 2 clinical trial reduced exacerbations by 60%–70% in patients on moderate dose ICS and a second controller.¹² All biomarkers of type-2 biology were suppressed including blood eosinophil count, FeNO and serum immunoglobulin E, suggesting a broader profile of action against the type-2 cytokine axis than currently available biologic therapies. In addition, in subjects with FeNO <24 ppb, a small but significant exacerbation reduction has been seen, raising the possibility that this treatment may impact exacerbations which are not primarily caused by type-2 inflammation.¹² Subsequently, this agent was awarded “breakthrough therapy designation” by the US Food and Drug Administration in September 2018⁵⁹; however, it remains to be seen if this promise is maintained in phase 3 of the clinical drug development. Clinical trials targeting another epithelial alarmin namely the IL33/ST2 axis are also currently in phase 2, and results are eagerly awaited.

Azithromycin taken regularly reduced moderate exacerbations in a large Australian study in moderate-to-severe asthma (AMAZES).⁶⁰ The definition of moderate exacerbations included episodes requiring antibiotics or increased medication usage but

FIGURE 3 The clinical challenge of T2-low severe asthma: an obese patient with a clinical diagnosis of asthma on high-dose treatment when assessed clinically with appropriate clinical investigations may have very different clinical outcomes, and in the absence of precise biomarkers to define non-T2 mechanism in asthma/T2-low asthma, precise clinical phenotyping will be required to ensure both adequate clinical assessment and meaningful mechanistic investigation. '..... *This patient may have treated T2-asthma but the exercise-induced bronchoconstriction is probably independent of T2-inflammation, that is a T2-low mechanism



importantly in a predefined post hoc analysis azithromycin reduced severe exacerbations requiring rescue systemic corticosteroids. Of interest, the treatment benefit of azithromycin was reported to be seen in subjects with both eosinophilic and noneosinophilic asthma where noneosinophilic asthma was defined by sputum eosinophil count of less than 3% at study entry or, if sputum was unavailable, a blood eosinophil count of less than 300/ μ L. This would suggest that this intervention potentially works in all patients with asthma who remain exacerbation prone despite background ICS treatment including those with T2-high phenotype. However, widespread use of this approach needs to be weighed up against the potential for antibiotic resistance, which is a recognized problem with regular macrolide use, but in subgroups of patients where there are persistent or frequent bacterial isolates, this is a clinically useful strategy.

Other interventions putatively targeting non-type-2 inflammation in asthma including IL-17 and CXCR2 have thus far been disappointing in clinical trials but importantly, these trials did not preselect on the basis of the relevant target being both upregulated and causal in recruited patients with asthma.^{61,62} It has been suggested that IL-17 and IL-13 are reciprocally regulated in asthma which may mean that targeting these inflammatory pathways together may be advantageous but the reduced efficacy in targeting IL-13 alone has potentially questioned the efficacy of this strategy.⁶³

There has been interest in a potential role of IL-6 in severe asthma and other pulmonary disease.⁶⁴ Data from the Severe Asthma Research Programme (SARP) in the United States have suggested that elevated IL-6 is seen predominantly in obese patients with asthma and is associated with metabolic dysfunction including elevated CRP and neutrophil leucocytosis.⁶⁵ Of note, lung function was lower in IL6-high patients, including those who were not obese, but the precise mechanism remains to be established

and whether this is an effect on lung function which is independent of having asthma. Data from the Seinäjoki Asthma Study in Finland also reported high circulating levels of CRP and/or IL-6 in adult-onset asthma patients with multiple comorbidities noting association with female gender, higher body mass index, greater smoking pack-years and poor asthma control with worse lung function, again linking comorbidity, elevated IL-6 and CRP with poor asthma control.⁶⁶ However, elevated IL-6 is associated with metabolic dysfunction in other disease areas and the question remains whether the elevated IL-6 is related to metabolic dysfunction in a subgroup of severe asthma patients than specifically to asthma.⁶⁷⁻⁶⁹

Bronchial thermoplasty is a physical rather than pharmacological modality shown to have a small clinical benefit, but in the context of a large placebo effect.⁷⁰⁻⁷² It is thought to reduce the bronchial smooth muscle mass that contributes to airflow obstruction in chronic asthma, although the exact mechanism of action and the phenotype most likely to benefit from this treatment have yet to be defined. Interestingly, unlike the monoclonal antibodies where cessation of treatment is associated with clinical relapse,^{73,74} there is some evidence that the beneficial effects of thermoplasty may be longer lasting postprocedure with an improvement in exacerbation rate maintained at 5 years post-treatment in the AIR2 trial,⁷¹ although unfortunately outcome data for the placebo arm of this trial are not available.

5 | THE CHALLENGE OF DEFINING T2-LOW SEVERE ASTHMA

As discussed above, T2-low asthma has been most clearly described in mild disease where suppression of background type-2 inflammation

is not confounded by current ICS treatment. The mechanism of this asthma endotype remains unclear and is potentially heterogeneous. It may involve different inflammatory processes, for example, driven by IL17, IL6, IL23 or other inflammatory pathways or be independent of a specific inflammatory process and instead be due to airway smooth muscle or neural dysfunction. It is also likely that in some patients, other factors such as bacterial infection, other environmental exposures and extra-pulmonary host factors, for example obesity, may be important in driving persistent symptoms which are not specifically asthma related. Accurate clinical phenotyping and defining the precise mechanism underlying symptoms in individual patients is critical to unravelling the complex heterogeneity seen regularly in any severe asthma clinic.

This heterogeneity and the clinical challenge of unravelling this complexity in the clinic are illustrated in Figure 3. If one considers a new patient referral with "difficult-to-control" asthma (Figure 3 and Box 1), on high-dose treatment with persistent symptoms, low for biomarkers of type-2 inflammation and might thus be considered to have little evidence of inflammation responsive to therapies targeting this inflammatory axis or "type-2 low" asthma. However, if further investigations are performed, different clinical outcomes may emerge which are very different in both defining the clinical problem and specific inflammatory endotype. We have previously shown that cardiopulmonary exercise testing is useful in discriminating patients with exercise-induced airflow obstruction or ventilatory limitation from other nonasthma factors or conditions, which limit exercise tolerance (including hyperventilation, physical deconditioning and submaximal effort) and which can be defined physiologically on the basis of exercise testing.⁷⁵ However, lung mechanics are altered in obesity, with a lower functional residual capacity and tidal volume, which unloads airway smooth muscle causing more fibre shortening during bronchoconstriction^{76,77}; thus, determining the precise mechanism of exertional limitation is important.

In many of these patients, when it is established that asthma is not the limiting factor, treatment can be substantially reduced, especially corticosteroid treatment. If treatment is withdrawn, it may be the case that markers of type-2 inflammation become apparent, in which case treatment might reasonably be optimized using these markers as treatment guidance.⁷⁸ However, it is also possible that type-2 biomarkers remain low despite complete withdrawal of ICS treatment, and at this stage, a measure of bronchial hyperresponsiveness should be undertaken to confirm a diagnosis of asthma. It is recognized that a substantial minority of patients with a label of asthma, and taking regular treatment, will have little evidence of underlying asthma when treatment is withdrawn.⁷⁹

6 | SUMMARY

It is now recognized that severe asthma is a complex clinical syndrome and multiple comorbidities are prevalent and associated with poorer asthma outcomes. Poor adherence to inhaled medication is widespread in difficult-to-treat severe asthma and cannot be detected subjectively. Short-term profiling of the biomarker responses

to monitored inhaled treatment, particularly ICS, in subjects with difficult-to-control severe asthma is a helpful part of clinical phenotyping. Monitoring helps to dichotomize those likely to respond to higher-dose ICS/long-acting beta-agonist therapy when used regularly, from those who, despite good adherence with inhaled treatment, are likely to require additional treatment. A systematic multidisciplinary approach in a specialist service is a good clinical model to comprehensively address all these issues and is associated with improved patient outcomes.

We currently have clinically useful biomarkers of T2-high asthma specifically sputum eosinophil counts, blood eosinophil counts and FeNO. Of these, blood eosinophil count and FeNO have performed remarkably well as prognostic markers of risk for severe exacerbations, predictive markers of corticosteroid responsiveness and predictive markers of response to novel biologic therapies targeting the type-2 cytokine axis to the extent that sputum eosinophilia will become largely obsolete outside a research setting or to assist in specifically challenging clinical cases. FeNO and blood eosinophil count have also helped define thresholds where we can exclude type-2 biology at a given time.

We are struggling to identify biomarkers of T2-low asthma, and currently, we define this as a patient with asthma and persistent poor control who does not have evidence of T2 inflammation (bronchoscopic sampling, sputum) or related biomarkers (FeNO, blood eosinophil count) at that point in time. It is recognized that background ICS treatment suppresses type-2 inflammation and these associated biomarkers. The precise mechanisms of asthma pathophysiology, which is not mediated by type-2 cytokine-driven inflammation, remain to be more clearly defined. Precise clinical phenotyping and accurate dissection of the clinical problem are required to understand the mechanism of persistent symptoms in an individual patient prior to assigning a rather arbitrary label of T2-low asthma. This would be best achieved by a consensus approach to clinical assessment and definitions accepting that the T2-low population is likely to be heterogeneous with multiple extra-pulmonary factors, which are not asthma, likely to be involved in the overall symptom complex.

ORCID

P. Jane McDowell  <https://orcid.org/0000-0003-2063-7992>

Liam G. Heaney  <https://orcid.org/0000-0002-9176-5564>

REFERENCES

1. Brown HM. Treatment of chronic asthma with prednisolone: significance of eosinophils in the sputum. *Lancet*. 1958;2:1245-1247.
2. Controlled trial of effects of cortisone acetate in chronic asthma: report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. *Lancet*. 1956;268(6947):798-803.
3. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet*. 1999;353(9171):2213-2214.
4. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180(5):388-395.

5. McGrath KW, Icitovic N, Boushey HA, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med*. 2012;185(6):612-619.
6. Arron JR, Scheerens H, Matthews JG. Redefining approaches to asthma: developing targeted biologic therapies. *Adv Pharmacol*. 2013;66:1-49.
7. Heaney LG, Djukanovic R, Woodcock A, et al. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). *Thorax*. 2016;71(2):187-189.
8. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol*. 2013;132(4):821-827.e5.
9. Mogensen I, Alving K, Bjerg A, et al. Simultaneously elevated exhaled nitric oxide and serum-eosinophil cationic protein relate to recent asthma events in asthmatics in a cross-sectional population-based study. *Clin Exp Allergy*. 2016;46(12):1540-1548.
10. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31-44.
11. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
12. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.
13. Global Initiative for Asthma. GINA guideline: Difficult to treat and severe asthma in adolescent and adult patients. Diagnosis and management 2018. <https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf>. Accessed May 9, 2019.
14. Evans PM, O'Connor BJ, Fuller RW, Barnes PJ, Chung KF. Effect of inhaled corticosteroids on peripheral blood eosinophil counts and density profiles in asthma. *J Allergy Clin Immunol*. 1993;91(2):643-650.
15. Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med*. 2005;172(4):453-459.
16. Mukherjee M, Nair P. Blood or sputum eosinophils to guide asthma therapy? *Lancet Respir Med*. 2015;3(11):824-825.
17. Hanratty CE, Matthews JG, Arron JR, et al. A randomised pragmatic trial of corticosteroid optimization in severe asthma using a composite biomarker algorithm to adjust corticosteroid dose versus standard care: study protocol for a randomised trial. *Trials*. 2018;19(1):5.
18. Heaney LG. Cough and severe asthma. *Pulm Pharmacol Ther*. 2017;47:72-76.
19. Heaney LG, Conway E, Kelly C, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax*. 2003;58(7):561-566.
20. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J*. 2003;22(3):478-483.
21. Agustí A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47(2):410-419.
22. Tay TR, Hew M. Comorbid, "treatable traits" in difficult asthma: current evidence and clinical evaluation. *Allergy*. 2018;73(7):1369-1382.
23. ten Brinke A, Sterk PJ, Masclee AA, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J*. 2005;26(5):812-818.
24. Bel EH, Sousa A, Fleming L, et al. Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, consensus generation, diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax*. 2011;66(10):910-917.
25. Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol*. 2014;134(6):1260-1268.
26. Bender B, Pedan A, Varasteh L. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol*. 2006;118(4):899-904.
27. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2009;180(9):817-822.
28. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax*. 2012;67(8):751-753.
29. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135:896-902.
30. Royal College of Physicians. National review of asthma deaths, 2014. <https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths>. Accessed Nov 11, 2018.
31. Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax*. 2012;67:268-270.
32. Bracken M, Fleming L, Hall P, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child*. 2009;94:780.
33. Sweeney J, Patterson CC, Menzies-Gow A, et al. British Thoracic Society Difficult Asthma Network Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax*. 2016;71(4):339-346.
34. Bloechliger M, Reinau D, Spoendlin J, et al. Adverse events profile of oral corticosteroids among asthma patients in the UK: cohort study with a nested case-control analysis. *Respir Res*. 2018;19(1):75.
35. Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respir Res*. 2017;18(1):129.
36. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med*. 2018;378(20):1865-1876.
37. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877-2188.
38. Dweik RA, Boggs PB, Erzurum SC, et al. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602-615.
39. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2012;186(11):1102-1108.
40. Heaney LG, Busby J, Bradding P, et al. Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. *Am J Respir Crit Care Med*. 2019;199(4):454-464.
41. Bender BG. Sorting out nonadherence and airway inflammation in treatment escalation for severe asthma. *Am J Respir Crit Care Med*. 2019;199(4):400-402.
42. Thakkar J, Kurup R, Laba TL, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA Intern Med*. 2016;176(3):340-349.
43. Tran N, Coffman JM, Sumino K, Cabana MD. Patient reminder systems and asthma medication adherence: a systematic review. *J Asthma*. 2014;51(5):536-543.
44. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;21:9.

45. Bel EH, Wenzel SE, Thompson PJ, et al. SIRIUS Investigators Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197.
46. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
47. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTAL): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med*. 2016;4(10):781-796.
48. Panettieri Jr RA, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med*. 2018;6(7):511-525.
49. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485.
50. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659.
51. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207.
52. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
53. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
54. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355-366.
55. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804-811.
56. Casale T, Chipps B, Rosén K, Trzaskoma B, Haselkorn T, Omachi A. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy*. 2018;73(2):490-497.
57. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7(1):156-164.e1.
58. Humbert M, Taillé C, Mala L, Gros VL, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J*. 2018;51(5):1702523.
59. Food and Drug Administration News. FDA awards AstraZeneca and Amgen's Tezepelumab breakthrough design 2018. <https://www.fdanews.com/articles/188355-fda-awards-astrazeneca-and-amgens-tezepelumab-breakthrough-designation>. Accessed December 28, 2018.
60. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390(10095):659-668.
61. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med*. 2013;188(11):1294-1302.
62. O'Byrne PM, Metev H, Puu M, et al. Efficacy and safety of a CXCR6 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2016;4(10):797-806.
63. Choy DF, Hart KM, Borthwick LA, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med*. 2015;7(301):301ra129.
64. Rincon M, Irvin CG. Role of IL-6 in asthma and other inflammatory pulmonary diseases. *Int J Biol Sci*. 2012;8(9):1281-1290.
65. Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Lancet Respir Med*. 2016;4(7):574-575.
66. Ilmarinen P, Tuomisto LE, Niemelä O, et al. Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. *Eur Respir J*. 2016;48:1052-1062.
67. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab*. 2001;280:E745-E751.
68. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia*. 1997;40:1286-1292.
69. Eder K, Baffy N, Falus A, Fulop A. The major inflammatory mediator interleukin-6 and obesity. *Inflamm Res*. 2009;58:727-736.
70. Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med*. 2007;356(13):1327-1337.
71. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma. *Am J Respir Crit Care Med*. 2010;181(2):116-124.
72. Cochrane review. Bronchial thermoplasty for people with asthma. https://www.cochrane.org/CD009910/AIRWAYS_bronchial-thermoplasty-for-people-with-asthma. Accessed May 01 2019.
73. Halder P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol*. 2014;133(3):921-923.
74. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.
75. McNicholl DM, Megarry J, McGarvey LP, Riley MS, Heaney LG. The utility of cardiopulmonary exercise testing in difficult asthma. *Chest*. 2011;139(5):1117-1123.
76. Ali Z, Ulrik CS. Obesity and asthma: A coincidence or a causal relationship? A systematic review. *Respir Med*. 2013;107(9):1287-1300.
77. Shore S, Fredberg J. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol*. 2005;115(5):925-927.
78. Petsky HL, Cates CJ, Kew KM, Chang AB. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. *Thorax*. 2018;73(12):1110-1119.
79. Aaron SD, Vandemheen KL, FitzGerald JM, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA*. 2017;317(3):269-279.

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