




Asthma Exacerbations in Severe Asthma: Why Systemic Corticosteroids May not Always Be the Best Treatment Option

P. Jane McDowell, PhD MBBS¹ 
J. Busby, PHD²
Liam G. Heaney, MD^{1*}

Address

^{1,2}Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK
Email: l.heaney@qub.ac.uk

²Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK

Published online: 25 February 2023

© The Author(s) 2023

This article is part of the Topical Collection on *Allergic Asthma*.

Keywords Asthma · Exacerbation · Phenotyping · T2 inflammation · Corticosteroids · Corticosteroid toxicity

Abstract

Purpose Advances in the management of severe, eosinophilic asthma have improved, but asthma exacerbations continue to occur. This review aims to look at the evidence we have about why exacerbations may occur; their phenotype and why oral corticosteroids may not always be the best treatment option for all exacerbation of symptoms in individuals with severe asthma.

Recent findings Studies dating back to the 1990s showed that asthma exacerbations across the spectrum of asthma severity were of different inflammatory endotypes. In addition, there is a wealth of evidence suggesting that eosinophilic inflammation is very responsive to corticosteroid therapy, but that non-eosinophilic inflammation is less so. Two recent UK-based studies have undertaken systematic phenotyping of exacerbations in severe asthma and have shown that there are a significant minority of exacerbation events with an increase in asthma symptoms, fall in lung function, but without evidence of raised T2 biomarkers.

Summary The evidence to date would suggest that T2 biomarker low asthma exacerbations do not benefit from the administration of oral corticosteroids; in fact, the effect of the oral corticosteroids is harmful. However, there is a paucity of data to answer this question directly. Further research is needed to assess the evolution of non-T2 exacerbations not treated with OCS in a randomised, placebo-controlled, manner.

Introduction

Treatment strategies to achieve asthma control have developed with the evolving understanding of the pathobiology of asthma. Early descriptions of asthma were of paroxysmal breathlessness which was later recognised to be due to bronchial hyperresponsiveness causing variable airways obstruction; therefore, initial treatments focused on agents that result in bronchodilatation, including theophylline, ephedrine and isoprenaline, and then more selective beta2-agonists, some of which are still used today [1, 2].

Improvement in asthma symptoms with the use of corticosteroids in those with evidence of airways eosinophilia [3] led to more widespread use of corticosteroid treatment, with the subsequent development of inhaled corticosteroid (ICS) therapy [4, 5], and the identification of eosinophilic inflammation in the airways as the major pathological process. In parallel, asthma management guidelines evolved to incorporate the earlier introduction of anti-inflammatory therapy to treatment regimes in a step-wise [6, 7] manner within this paradigm. In the past, patients

with persisting poor control, despite good adherence to maximal doses of ICS and long-acting bronchodilator treatment, would often end up on low dose maintenance oral corticosteroids (OCS) or have frequent OCS bursts for exacerbations. However, the well-recognised burden of OCS-related toxicities within these OCS-treated asthma populations [8–10] fuelled the drive for a greater understanding of the precise mechanisms of inflammation to allow for the development of targeted immune therapies. The development of efficacious, targeted anti-T2 agents has transformed the treatment of severe asthma (anti-IgE, anti-IL5/5R, anti-IL4R, and anti-TSLP), reducing asthma exacerbations by around 50% [11–15] and facilitating reduction of maintenance OCS (mepolizumab, benralizumab, and dupilumab) [11–13], thereby substantially reducing OCS exposure. However, despite these significant advances with treatments, which remove T2-eosinophilic inflammation, patients with severe asthma continue to have exacerbations, which has led to a focus on the additional mechanisms underlying these clinical events.

Heterogeneity of Asthma Exacerbations

A number of studies in the 1990s assessed the inflammatory phenotype of asthma exacerbations using sputum expectorated at the time of exacerbation [16–20]. Although the definition of sputum eosinophilia and neutrophilia, the inclusion criteria, and the population sampled varied between these different studies, they all demonstrated heterogeneity of airway inflammation at times of increased asthma symptoms seen across the spectrum of asthma severity from mild to severe exacerbations. Furthermore, it was clear that the inflammatory response in the airways was generally reproducible with the same trigger of exacerbation, for example, neutrophilic airways inflammation with viral triggers, or eosinophilic airways inflammation with allergen exposure [21].

In parallel, more easily measured biomarkers (specifically fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophil count) have

emerged as robust proxy markers of T2-driven eosinophilic airways inflammation and as prognostic markers for exacerbation and predictive markers of therapeutic response (corticosteroids and novel T2-biologics). These biomarkers have also been shown to be of value in the phenotyping process in all severities of asthma to allow better treatment choices [22–24, 25••, 26••] but outside of severe asthma, have not yet been widely adopted in clinical practice.

Recent evidence has further demonstrated substantial heterogeneity in asthma exacerbations in adult patients with severe asthma. Using FeNO and peripheral blood eosinophil counts, 71 exacerbations were phenotyped in a severe asthma population enriched for a T2-biomarker low (T2 low) population. An exacerbation visit was undertaken when the patient felt their asthma symptoms were outside of their normal daily variation, at the point where they would seek medical review or follow their personalised asthma action plan. T2 low exacerbations (FeNO ≤ 20 ppb and blood eos ≤ 150 cells/ μ L) were compared to those with evidence of T2 inflammation, T2 high (FeNO > 20 ppb or blood eos > 150 cells/ μ L) at the time of increased symptoms. Nineteen of 71 (26.7%) exacerbations were T2 low but notably, both T2 high and T2 low reported a similar increase in symptom burden (increase in ACQ7 T2 low 1.4 (0.8) versus T2 high 1.3 (0.8), $p = 0.72$) and had a similar fall in lung function (both groups had a mean FEV₁ (L) drop of -0.2 L (T2 low -0.2 (0.4), T2 high -0.2 (0.3), $p = 0.93$) from the clinically stable state to exacerbation suggesting that there was evidence of increased asthma symptoms and fall in lung function in the absence of T2 driven airways inflammation [25••].

In another study characterising exacerbations in a severe asthma population established on anti-IL5 therapy (mepolizumab), a sputum eosinophil count of $\geq 2\%$ was used to delineate the presence of eosinophilic inflammation at exacerbation. In this study, half of the exacerbations on mepolizumab were non-eosinophilic (sputum eosinophils $< 2\%$), and half had sputum eosinophils $\geq 2\%$. However, again exacerbations in both groups were associated with a similar fall in FEV₁ from baseline to exacerbation (delta change in FEV₁% from stable to exacerbation, sputum eosinophils $< 2\%$ group = -10.6% ($-16.2, -4.9$), versus sputum eosinophils $\geq 2\%$ group = -15.1% ($-22.9, -4.7$), 95% CI $-12.9, 5.0$, $p = 0.31$). Of note, the group with low sputum eosinophil count had a greater increase in sputum neutrophils at exacerbation, a higher CRP, and was more likely to have an infectious agent identified on sputum PCR (pathogenic virus or bacteria). Again, ACQ-5 increase and fall in lung function in both groups was comparable, highlighting the fact that non-eosinophilic exacerbations are clinically indistinguishable in terms of symptoms or fall in lung function and supports the need for phenotyping at the time of exacerbation [26••]. In this study, FeNO was useful in phenotyping eosinophilic and non-eosinophilic exacerbations; a FeNO ≤ 20 ppb had a 100% negative predictive value (95% CI 80, 100) for a sputum eosinophil $< 2\%$ at exacerbation, while FeNO ≥ 50 ppb had a positive predictive value of 77% (95% CI 60–90%) for a sputum eosinophil count of $\geq 2\%$ at exacerbation. Furthermore, a microbiome analysis from both aforementioned studies showed that a FeNO ≥ 50 ppb was associated with proteobacteria-low, alpha-diversity high microbial profile [27]. The inverse

relationship between FeNO and the presence of proteobacteria has previously been reported [28]. Taken together, this reinforces the use of FeNO as a point of care test at exacerbation, to highlight the presence of T2 high inflammation likely to be OCS-responsive, and the reduced likelihood of an exacerbation driven by infectious microorganisms. This study of exacerbation phenotyping is being replicated in benralizumab-treated severe asthmatics; the results are awaited (<https://clinicaltrials.gov/ct2/show/NCT04102800>).

Multiple studies have demonstrated the benefit of corticosteroids, to improve asthma control or reduce exacerbations, is only seen in those with evidence of T2-driven eosinophilic airways inflammation [3, 18, 29–32]. In contrast [3, 18, 29, 30], non-eosinophilic asthma has little response to corticosteroids [33, 34] suggesting that corticosteroids will have little benefit in non-T2/non-eosinophilic exacerbations. This hypothesis needs to be formally tested in a clinical trial which phenotypes exacerbations using rapid diagnostic tests and withholds systemic corticosteroids where there is no evidence of T2-inflammation. FeNO is already available for this type of study, but rapid turnaround of peripheral blood eosinophil count or use of a surrogate measure, e.g., point of care blood count tests [35], may also provide a mechanism to avoid unnecessary corticosteroid exposure. In parallel, given the prevalence of infective pathogens seen in exacerbations in T2-low severe asthma, this approach might be extended to use of rapid diagnostics in spontaneous sputum samples, where available, to determine if pathogenic bacterial and viral pathogens are present, which might also assist in directing appropriate use of antibiotics.

Consequences of Exacerbations

Asthma exacerbations are critically important events, implicated in airway remodelling, loss of lung function, and worse quality of life with economic consequences both to the individual patient and the health economy [36–39]. Asthma exacerbations are particularly important in those with severe asthma, although only ~3.7% of the whole asthma population [40]; they consume over 60% of the costs associated with asthma with significant unscheduled care utilisation [40]. The problem of recurrent exacerbations in severe asthma is a global one. A recent publication from the International Severe Asthma Registry (ISAR) included 4990 severe asthma patients and reported that 25% had ≥ 4 exacerbations per year, with a mean exacerbation rate of 1.7 (2.7)/year [41]. The repeated cycle of poor asthma control and exacerbations treated with OCS is associated with synergistic physiological consequences to the patient.

- Firstly, uncontrolled asthma/recurrent exacerbations are associated with airway remodelling and loss of lung function. The rate of lung function decline has been shown to be inversely proportional to age, further underlining the cruciality of early intervention in the case of recurrent exacerbations in young patients, and the need for timely referral to specialist care [42]. To date lung function decline has been shown to be largely non-reversible, [43] even when disease control is achieved in these patients, e.g., on starting a biologic, lung function may improve a little, but does not return to the pre-disease state as targeted biological therapies treat inflammation rather than structural change [12–14, 44]. Exacerbations and uncontrolled disease therefore result in structural change and lung function impairment.

- Secondly, the consequence of OCS use is by no means insignificant. A previous study of 2 large UK-based registries has shown that even as little as one course of OCS/year on top of background high dose ICS resulted in a statistically significant increase in corticosteroid-induced morbidity. [45] The toxicities associated with OCS use are ubiquitous and well documented; in a study that quantified toxicity associated with OCS use in 101 severe asthmatics about to commence biologics, every single patient had evidence of OCS toxicity, with toxicity burden varying between individuals [8]. OCS use to treat exacerbations leads to the development of OCS-related toxicities and can make disease control more difficult, e.g., weight gain, increased risk of infection, impaired glucose control, increased anxiety, and depression [39, 45–47].

There is ample evidence for heterogeneity in airways inflammation at the time of exacerbation; there is robust evidence that in biologics as well as non-biologics treated severe asthma; there are increases in symptom burden and fall in lung function both in the presence and the absence of T2 biology. The question is how can we phenotype these patients, do they all need OCS treatment, and do we have the evidence base to comfortably address these questions?

Management of Asthma Exacerbations

Although there has been considerable improvement in treatment options for disease control in severe asthma and a significant reduction in exacerbations, asthma exacerbations still occur, and unfortunately, the mainstay of treatment for increased asthma symptoms remains OCS.

The assumption that asthma exacerbations are driven by corticosteroid-responsive T2 airways inflammation, along with the knowledge that lack of corticosteroid treatment at exacerbation has been linked to asthma deaths [48, 49], has driven a reflex response to prescribe OCS for all increase in asthma symptoms often without judicious clinical review and in the absence of phenotyping exacerbations prior to treatment.

The potential for avoidance of OCS at exacerbation is suggested by two recent studies of severe asthma exacerbations; one in a non-biologics setting [25••] and the other, exacerbations in the context of biologics-treated severe asthmatics [26••]. In the first, 97.4% (265/272) of reported episodes of increased asthma symptoms received OCS in non-specialist settings, in comparison to 71.2% (84/118, $p < 0.001$) reviewed by asthma specialists [25••]. In the second biologics-treated cohort, 91% (69/76) of those who sought non-specialist review or followed their personalised asthma action plan for increased symptoms received OCS in comparison to 63.5% (61/96, $p < 0.001$) of those who had specialist review prior to commencing treatment [26••].

This cultural generalisation of exacerbations being homogenous, corticosteroid-responsive inflammation is also reflected within the world of specialist asthma within our evidence-base. It has become apparent through phase III clinical trials of anti-T2 monoclonal antibodies that phenotyping patients is crucial for assessing the efficacy of targeted biological therapies, with monoclonal antibodies generally being more beneficial in cohorts with a high exacerbation rate and evidence of elevated biomarkers of T2 inflammation

[50, 51]. However, the inclusion criteria of phase III clinical trials state an exacerbation count which participants must meet, which is more often than not, a count of OCS bursts for asthma exacerbations and assumes that each OCS burst was given for an episode of T2 high asthma exacerbation. Similarly, OCS burst counts also form part of the access criteria for biologics in the UK as a proxy for identifying frequent T2 exacerbators likely to respond to anti-T2 biologics [52–55]. However, this does not consider that episodes of increased respiratory symptoms can be due to infections, exacerbations of sinus or nasal disease, dysfunctional breathing, or vocal cord dysfunction for example. Unfortunately, these are often managed ubiquitously with courses of OCS and labelled as exacerbations of severe asthma which loses the important delineation of the cause of worsening symptoms by not recognising the underlying pathology of the exacerbation event. It is unsurprising that infectious events are common in patients receiving local immunosuppressive agents (ICS); sometimes, systemic immunosuppressive agents (OCS, now less common) and the effects of biologics on airways immune defence are not yet entirely defined.

Ultimately, part of the problem in exacerbation management is that we do not have an adequate definition or nomenclature when discussing exacerbations. Defining exacerbations using oral steroids assumes that the steroids were appropriate and that the pathology is steroid responsive. Ideally, an ethos of phenotyping each exacerbation would enable more direct and appropriate therapy and the avoidance of inappropriate OCS exposure.

Could We Do Things Differently to Reduce Inappropriate Oral Corticosteroid Exposure?

Figure 1 outlines an approach to assessing a patient with severe asthma and an increase in symptoms. Firstly, to those who have increased symptoms but no significant fall in lung function. FeNO is useful to assess if the patient has uncontrolled symptoms due to T2 airways inflammation which needs further delineation as to whether this is due to poor inhaler technique or non-adherence meaning a lack of treatment delivery to the airways, or if the patient is not getting enough ICS and their maintenance treatment needs to be escalated. If a patient has increased symptoms in the context of stable lung function and a stable FeNO, other causes of the increased symptom burden should be considered and investigated as appropriate, and oral corticosteroids are not indicated for an acute asthma exacerbation (see Fig. 1).

Moving to the left side of the algorithm, if there is a fall in lung function, assess T2 biomarkers available including blood eosinophils and FeNO. If markers of T2 biology are raised in the context of increased symptoms and a fall in lung function, corticosteroid treatment (usually OCS in severe asthma) is indicated to reduce T2 inflammation, and the opportunity should be taken to assess inhaler technique, check adherence (which may include prescription counts of inhalers or digitalised adherence monitors such as FeNO suppression [56] or connected inhaler systems [57]), and lastly, to consider if the patient meets criteria for biological therapy, particularly if they already have good inhaler technique and are adherent to prescribed treatment. Our only treatment arsenal for

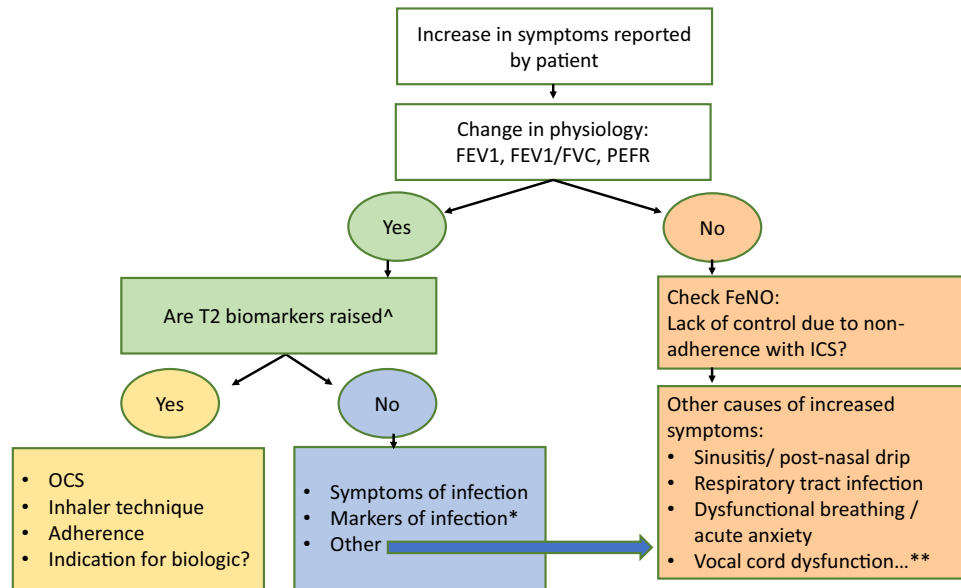


Fig. 1 Proposed approach to assessing acutely increased symptoms in an asthmatic patient. ^T2 biomarkers including FeNO and peripheral blood eosinophil count. *CRP, consolidative changes on chest Xray, positive sputum culture or viral swab. **This list is not exhaustive but serves to illustrate some differential diagnosis of increased symptoms with preserved lung function.

acute exacerbations driven by T2 inflammation is with corticosteroids; going forward, our collective aim should be to either develop targeted, non-corticosteroid treatments for episodes of acute T2 airways inflammation, or to have asthma management strategies that achieve remission of asthma disease so negating the regular use of OCS for treatment exacerbations [58].

The last group to discuss is those who have increased asthma symptoms, a fall in lung function with suppressed markers of T2 biology. This is likely to be the smallest group of patients in this algorithm, but as described in the exacerbation phenotyping studies above, this group of patients is present in severe asthma cohorts receiving anti-IL5 treatment, and in non-biologics treated severe asthmatics. Although evidence shows that OCS are not effective in the absence of T2 biology, and that OCS use induces morbidity, to date, there has not been a trial that assesses outcomes in non-T2 exacerbations not treated with OCS.

In the study, phenotyping exacerbations in a mepolizumab-treated subgroup (the MEX study [26]), T2 low exacerbations were statistically more likely to be associated with a viral or bacterial pathogen on PCR than T2 high exacerbations, but there is a paucity of information on the mechanisms of asthma exacerbations in the absence of T2 biology. With current knowledge, it is worth considering whether infection is the driving factor, treating infection as appropriate and consider down titrating corticosteroid treatment or the addition of azithromycin in the case of recurrent exacerbations [59].

Stability of exacerbation phenotype

Multiple trials, including the two described previously, [25••, 26••] have shown that the phenotype of exacerbations in an individual is not entirely stable across multiple exacerbations in that individual. Approximately, 75% of exacerbations will have the same phenotype at first and second exacerbations, but making treatment decisions based on phenotyping would require phenotyping at each exacerbation.

Conclusion

To summarise, increase in respiratory symptoms in a patient known to have asthma can occur for many reasons, and is not always synonymous with asthma exacerbations. When they do occur, asthma exacerbations are heterogenous in nature with evidence of eosinophilic and non-eosinophilic inflammation underlying. These can be differentiated at the time of increased symptoms using biomarkers including blood eosinophils, FeNO, and C-reactive protein. There is evidence that eosinophilic inflammation is very responsive to corticosteroid treatment, and non-eosinophilic inflammation less so. An urgent unmet research need is to assess the evolution of non-T2 asthma exacerbations not treated with OCS in a placebo-controlled trial. However, the holy grail of asthma treatment is to aim for disease remission where exacerbations of disease do not occur.

Declarations

Conflict of interest

Dr McDowell has received speaker's honoraria from GSK and support for attending meetings from Cheisi, outside the submitted work. Dr. Busby reports grants from AstraZeneca, personal fees from Nuvoair, outside the submitted work. Prof Heaney has received payment honoraria from LGH has received non-financial support from GlaxoSmithKline during the conduct of the study; has received grants from Amgen, AstraZeneca, Medimmune, Janssen, Novartis, Roche/Genentech, GlaxoSmithKline, Boehringer Ingelheim, Aerocrine, and Vitalograph; is the lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma in partnership with Novartis, Hoffman la Roche/Genentech, Evelo Biosciences, Sanofi, GlaxoSmithKline, AstraZeneca, Teva, Theravance, and Circassia; has received travel funding support for international respiratory meetings (institution remunerated) from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Napp Pharmaceutical; has received project grant funding from Medimmune, Novartis UK, Roche/Genentech, and GlaxoSmithKline; and has received funding for clinical trials (institution remunerated) from AstraZeneca, GlaxoSmithKline, Schering Plough, Synairgen, Novartis, and Roche/Genentech. These are outside of the submitted work.

Human and animal rights and informed consent

This article does not contain new study data with human or animal studies performed by any of the authors.

Open Access

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as: ●● Of major importance

- Holgate ST. A brief history of asthma and its mechanisms to modern concepts of disease pathogenesis. *Allergy Asthma Immunol Res.* 2010 May 6;2(3):165–71.
- Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. *The Lancet.* 2018 Jan 27;391(10118):350–400.
- Morrow Brown H. Treatment of chronic asthma with prednisolone significance of eosinophils in the sputum. *The Lancet.* 1958 Dec 13;272(7059):1245–7.
- Morrow Brown H, Storey G, George WHS. Papers and originals beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J.* 1972;1:585–90.
- Helm W, Heyworth F. Inhalation of hydrocortisone acetate for bronchial asthma. *Br Med J.* 1958;5(5099):768–9.
- Asthma | British Thoracic Society | Better lung health for all [Internet]. [cited 2022 Nov 9]. Available from: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>
- 2022 GINA Main Report - Global initiative for asthma - GINA [Internet]. [cited 2022 Nov 9]. Available from: <https://ginasthma.org/gina-reports/>
- McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Quantification of glucocorticoid-associated morbidity in severe asthma using the glucocorticoid toxicity index. *J Allergy Clin Immunol Pract.* 2020 Sep 1;9(1):365–72.
- Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol.* 2015 Dec 1;136(6):1488–95.
- Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015 Jun 1;100(6):2171–80.
- Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018 Jun 28;378(26):2486–96.
- Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker 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. *The Lancet.* 2016;388(10056):2115–27.
- Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, 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(5):355–66.
- Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *The Lancet.* 2012;380(9842):651–9.
- Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med.* 2021;384(19):1800–9.
- Tumer MO, Hussack P, Sears MR, Dolovich J, Hargreave FE. Exacerbations of asthma without sputum eosinophilia. *Thorax.* 1995;50(10):1057–61.
- Gibson PG, Simpson JL, Salto N. Heterogeneity of airway inflammation in persistent asthma: evidence of neutrophilic inflammation

- and increased sputum interleukin-8. *Chest*. 2001;119(5):1329–36.
18. Baigelman W. Sputum and blood eosinophils during corticosteroid treatment of acute exacerbations of asthma. *Am J Med*. 1983;75(6):929–36.
 19. Ordoñez C, Shaughnessy T, Matthay M, Fahy J. Increased neutrophil numbers and IL-8 in airway secretions in acute severe asthma: clinical and biological significance. *Am J Respir Crit Care Med*. 2000;161(4):1185–90.
 20. Fahy J v., Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol*. 1995 Apr;95(4):843–52.
 21. Wark PAB. Asthma exacerbations 3: Pathogenesis. *Thorax*. 2006;61:909–15.
 22. Shaw DE, Heaney LG, Thomas M, Beasley R, Gibson PG, Pavord ID. Balancing the needs of the many and the few: where next for adult asthma guidelines? *Lancet Respir Med*. 2021 Jul;9(7):786–94.
 23. Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med*. 2020;8(7):671–80.
 24. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med*. 2021;9(1):69–84.
 - 25.●● McDowell PJ, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker S, et al. Exacerbation profile and risk factors in a type-2-low enriched severe asthma cohort a clinical trial to assess asthma exacerbation phenotypes. *Am J Respir Crit Care Med*. 2022;206:545–53.
- Findings from this study show that around a quarter of exacerbations in a T2-low enriched severe asthma population, exhibit a fall in FEV1 along with a rise in ACQ5 without elevated T2 biomarkers.
- 26.●● McDowell PJ, Diver S, Yang F, Borg C, Busby J, Heaney LG, et al. The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med*. 2021;9(10):1174–84.
- Findings from this study show that T2 exacerbations occur in the absence of a rise in T2 biomarkers in a biologics treated group of severe asthmatics, and that FeNO is useful in phenotyping these exacerbations.
27. Diver S, Haldar K, McDowell PJ, Busby J, Mistry V, Micieli C, et al. Relationship between inflammatory status and microbial composition in severe asthma and during exacerbation. *Allergy*. 2022;77(11):3362–76.
 28. Huang YJ, Nariya S, Harris JM, Lynch SV, Choy DF, Arron JR, et al. The airway microbiome in patients with severe asthma: associations with disease features and severity. *J Allergy Clin Immunol*. 2015;136(4):874–84.
 29. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor R. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax*. 2010 May;65(5):384–90
 30. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol*. 2002 Mar 1;109(3):410–8.
 31. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2–driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180(5):388–95.
 32. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci*. 2007;104(40):15858–63.
 33. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet*. 1999 Jun 26;353(9171):2213–4.
 34. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med*. 2012 Mar 15;185(6):612–9.
 35. Hambleton K, Connolly CM, Borg C, Davies JH, Jeffers HP, Russell REK, et al. Comparison of the peripheral blood eosinophil count using near-patient testing and standard automated laboratory measurement in healthy, asthmatic and COPD subjects. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2771–5.
 36. McDonald VM, Gibson PG, Gibson PG. Exacerbations of severe asthma. *Clin Exp Allergy*. 2012;42:670–7.
 37. O’Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax*. 2015;70(4):376–8.
 38. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med*. 1997;156(3 I):787–93.
 39. Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. *Clin Ther*. 2011;33(10):1413–32.

40. GINA. GLOBAL INITIATIVE FOR ASTHMA A GINA Pocket Guide For Health Professionals DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescent and adult patients Diagnosis and Management A GINA Pocket Guide For Health Professionals DIFFICULT-TO-TREAT & SEVERE ASTHMA in adolescence. 2019 [cited 2020 Mar 13]. Available from: <https://www.ginasthma.org>
41. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry. *Chest*. 2020;157(4):790–804.
42. Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax*. 2022 Aug 3:1–10.
43. Matsunaga K, Hirano T, Oka A, Tanaka A, Kanai K, Kikuchi T, et al. Progression of irreversible airflow limitation in asthma: correlation with severe exacerbations. *J Allergy Clin Immunol Pract*. 2015;3(5):759–764.e1.
44. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018 Jun 28;378(26):2486–96.
45. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. 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):339–46.
46. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. 2018;52(4):1800703.
47. Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. 2015;136(6):1488–95.
48. Why asthma still kills The National Review of Asthma Deaths (NRAD). 2014 [cited 2022 Oct 23]; Available from: <https://www.rcplondon.ac.uk/nrad>
49. Suissa S, Ernst P, Boivin JE, Horwitz RI, Habbick B, Cockcroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med*. 2012 Dec 20;149(3 I):604–10.
50. Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med*. 2016;4(10):781–96.
51. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med*. 2007 Dec 1;176(11):1062–71.
52. Dupilumab for treating severe asthma with type 2 inflammation. 2021 [cited 2022 Oct 24]; Available from: <https://www.nice.org.uk/guidance/ta751>
53. Reslizumab for treating severe eosinophilic asthma. 2017 [cited 2022 Oct 24]; Available from: <https://www.nice.org.uk/guidance/ta479>
54. Benralizumab for treating severe eosinophilic asthma. 2019 [cited 2022 Oct 24]; Available from: <https://www.nice.org.uk/guidance/ta565>
55. Mepolizumab for treating severe eosinophilic asthma. 2021 [cited 2022 Oct 24]; Available from: www.nice.org.uk/guidance/ta671
56. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. *Am J Respir Crit Care Med*. 2019 Feb 15;199(4):454–64.
57. Moore A, Preece A, Sharma R, Heaney LG, Costello RW, Wise RA, et al. A randomised controlled trial of the effect of a connected inhaler system on medication adherence in uncontrolled asthmatic patients. *Eur Respir J*. 2021 Jun 4;57(6):2003103.
58. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145(3):757–65.
59. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, 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. *The Lancet*. 2017;390(10095):659–68.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.