

Asthma in the Biologics Era: Should Oral Corticosteroid Therapy Be Relegated to History?



Florence Schleich, MD, PhD^a, John J. Oppenheimer, MD^b, Guy Brusselle, MD, PhD, FERS^c, Liam G. Heaney, MD^d, William W. Busse, MD^e, Njira L. Lugogo, MD^f, Nicola A. Hanania, MD, MS^g, Matteo Bonini, MD, PhD^{h,i}, Marek Lommatzsch, MD^j, Pascal Chanez, MD, PhD^k, Anna Vichiendilokkul, PharmD, MS^l, Victoria S. Benson, PhD^m, Tricia Finney-Hayward, PhDⁿ, Peter Howarth, MBBS, DM, FRCPⁿ, and Elliot Israel, MD^o *Liège and Ghent, Belgium; Belfast and London, United Kingdom; Rome, Italy; Rostock, Germany; Marseille, France; Newark, N.J.; Madison, Wis; Ann Arbor, Mich; Houston, Texas; Pennsylvania, Pa; and Boston, Mass*

Oral corticosteroids (OCS) have been used for both maintenance and burst treatment of asthma since the 1950s owing to their beneficial effect on symptoms and exacerbations coupled with a historical lack of alternative therapies. Despite the current availability of well-tolerated and effective treatment with

biologics, chronic OCS use remains high. This is of great concern because evidence suggests that a lifetime cumulative exposure even as low as 0.5 to 1.0 g prednisolone equivalent (about three to four bursts of OCS) significantly increases the risk of a wide range of acute and long-term adverse effects, some

^aDepartment of Respiratory Medicine, CHU Liège, GIGA I Lab, University of Liège, Liège, Belgium

^bDepartment of Internal Medicine, UMDNJ Rutgers University School of Medicine, Newark, N.J.

^cDepartment of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

^dWellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, United Kingdom

^eDepartment of Medicine, University of Wisconsin School of Medicine, Madison, Wis

^fDivision of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Mich

^gSection of Pulmonary, Critical Care, and Sleep Medicine, Baylor College of Medicine, Houston, Texas

^hDepartment of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

ⁱNational Health and Lung Institute (NHLI), Imperial College London, London, United Kingdom

^jDepartment of Pneumology, University of Rostock, Rostock, Germany

^kDepartment of Respiratory Diseases, Aix-Marseille Université, INSERM, INRAE, C2VN, Marseille, France

^lClinical Science, GSK, Collegeville, Pennsylvania, Pa

^mGlobal Epidemiology, GSK, London, United Kingdom

ⁿGlobal Medical Affairs, GSK, London, United Kingdom

^oPulmonary and Critical Care Medicine, Allergy & Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

Conflicts of interest: F. Schleich received support from AstraZeneca, Chiesi, GSK, and Sanofi; and lecture fees from AstraZeneca, Chiesi, GSK, Novartis, and Teva. J.J. Oppenheimer has received honoraria and/or consulting fees from Amgen, Aquestive, AstraZeneca, Novartis, GSK, Sanofi, and Regeneron. G. Brusselle has received honoraria for advisory boards and speaker's fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Merck Sharp & Dohme, Novartis, Sanofi, and Regeneron. L.G. Heaney has received grant funding, participated in advisory boards, and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GSK, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; has received grants from MedImmune, Novartis UK, Roche, Genentech Inc., GSK, Amgen, Hoffman la Roche, AstraZeneca, Aerocrine, and Vitalograph; has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Napp Pharmaceuticals; has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GSK for which his institution received remuneration; and is the academic lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GSK, Hoffmann la Roche, and Janssen. W.W. Busse has received royalties/

licenses from Elsevier, as well as payments, honoraria, consulting fees, and support for attending meetings and/or travel from Sanofi, GSK, and Regeneron. N.L. Lugogo received consulting fees from Amgen, AstraZeneca, Avillion, Genentech, GSK, Niox, Novartis, Regeneron, Sanofi, and Teva; honoraria for non-speakers bureau presentations from GSK, Teva, and AstraZeneca; and travel support from AstraZeneca, Sanofi, Teva, Regeneron, and GSK; her institution received research support from Amgen, AstraZeneca, Avillion, Bellus, Evidera, Gossamer Bio, Genentech, GSK, Janssen, Niox, Regeneron, Sanofi, Novartis, and Teva. She is an honorary faculty member of Observational and Pragmatic Research Institute but does not receive compensation for this role. N.A. Hanania receives honoraria for serving as a consultant or on advisory boards for GSK, AstraZeneca, Sanofi, Regeneron, Genentech, and Amgen. His institution receives research grant support on his behalf from GSK, AstraZeneca, Sanofi, Regeneron, Chiesi, and Genentech. M. Bonini has received research grants, advisory board, expert consultancy, and lecture fees from AstraZeneca, Chiesi, Grifols, GSK, Lallemand, Lusofarmaco, Menarini, Omron, and Sanofi. M. Lommatzsch reports grants for research or clinical trials, paid to his institution, from AstraZeneca, Deutsche Forschungsgemeinschaft, and GSK; and consulting fees, travel expenses, or honoraria for lectures from ALK, Allergopharma, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GSK, HAL Allergy, Leti, Novartis, Merck Sharp & Dohme, Sanofi, Stallergenes, and Teva. P. Chanez is an advisor for Boehringer Ingelheim, Boston Scientific, GSK, AstraZeneca, Novartis, Teva, Chiesi, Sanofi, and SNCF; has received advisory board fees and/or honoraria from Boehringer Ingelheim, GSK, AstraZeneca, Novartis, Teva, Chiesi, Boston Scientific, ALK, AB Science, Argenx, and Sanofi; has received grants from Roche, Boston Scientific, Boehringer Ingelheim, GSK, AstraZeneca, ALK, and Novartis; and is the elected president of the Scientific Committee de la Fondation du Souffle (2020-2025). A. Vichiendilokkul, V.S. Benson, T. Finney-Hayward, and P. Howarth are employed by GSK and hold financial equities in GSK. E. Israel has received research grants from AstraZeneca and NIH; has received advisory board fees and/or honoraria from AstraZeneca, Amgen, Sanofi, Merck, Regeneron, Teva, Apogee Therapeutics, Arrowhead Therapeutics, Yuhan, GSK, Generate Biomedicine, and Jasper Therapeutics; and has received study drugs for studies from Genentech, Sun Pharma, Laurel Pharmaceuticals, Om Pharma, Nestle, and CSL Behring.

Received for publication September 30, 2024; revised March 25, 2025; accepted for publication April 3, 2025.

Available online April 11, 2025.

Corresponding author: Florence Schleich, MD, PhD, Department of Respiratory Medicine, CHU Liège, GIGA I³ Lab, University of Liège, Av Hippocrate 1/11, Liège 4000, Belgium. E-mail: fschleich@chuliege.be.

2213-2198

© 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2025.04.007>

Abbreviations used

AE- Adverse event
 FeNO- fraction of exhaled nitric oxide
 GINA- Global Initiative for Asthma
 GTI- Glucocorticoid Toxicity Index
 HCP- Health care professional
 Ig E- immunoglobulin E
 IL- interleukin
 mOCS- Maintenance OCS
 OCS- Oral corticosteroid
 PCP- Primary care physician
 QoL- Quality of life

of which may not be fully reversible. Conversely, biologics have demonstrated a more favorable benefit-risk profile compared with OCS, while reducing exacerbations and improving symptom control. Here, we review the current situation, highlight the need for improved stewardship of OCS use, describe the cumulative and potentially irreversible toxicity seen with even short bursts of OCS, and discuss the role of biologics in minimizing their use. Finally, we provide our opinion on how maintenance OCS therapy in asthma can be relegated to history, with early patient risk evaluation to identify and measure biomarkers and/or clinical traits that may predict risk of future exacerbations, enabling proactive preventative intervention. © 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2025;13:1559-68)

Key words: Asthma; Oral corticosteroids; Burst; Maintenance; Adverse effect; Safety; Biologic; Targeted therapies; IL-5; Precision medicine

INTRODUCTION

Systemic corticosteroids, generally administered orally (oral corticosteroids [OCS]), were first used clinically in the 1950s and have since been employed to manage various chronic inflammatory diseases, including asthma.¹⁻⁵ Although the current approach to asthma management primarily relies on inhaled corticosteroids (either as monotherapy or combination therapy) to minimize systemic bioavailability and deliver drug to the target site within the airways,⁶ OCS remain important for some patients with severe asthma as either a long-term (maintenance OCS [mOCS]) therapy or recurrent short-term (burst) therapy to manage exacerbations.^{3,4} Adverse events (AEs) with OCS are well appreciated and were noted as early as 1953.⁷ Oral corticosteroids are known to increase the risk of a range of both acute and chronic AEs even at a relatively low exposure.⁸⁻¹¹ Despite this, OCS continue to be used in asthma management partly owing to beneficial effects such as improved symptom control and exacerbation relief,^{7,12,13} but primarily to a historical lack of alternative therapies and current lack of access to biologics in some countries.¹⁴

The terms mOCS and burst OCS are not always consistently defined in the literature. According to the Global Initiative for Asthma (GINA) and National Heart, Lung, and Blood Institute guidelines,^{3,4} mOCS refers to chronic therapy taken on a daily or

regular basis for an indefinite period or more than 28 consecutive days, whereas burst OCS indicates acute therapy taken for a defined period to treat an asthma exacerbation. The Global Initiative for Asthma describes this defined period as about 5 to 7 days (40-50 mg/day in adults and 1-2 mg/kg in children [maximum 40 mg]).³ However, clinical trials (supported by European Respiratory Society/American Thoracic Society guidelines)¹⁵ more commonly define burst use as 3 or more days of OCS (indeed, receipt of temporary OCS at a higher dose than maintenance therapy often forms part of the definition of a severe exacerbation in such trials).¹⁶⁻¹⁸

Currently, six biologic therapies are available, including anti-immunoglobulin E (IgE), anti-interleukin (IL)-5/IL-5R, anti-IL-4R α /13, and anti-thymic stromal lymphopoietin.^{3,19} These biologics are recommended by both GINA and Expert Panel Working Group of the National Heart, Lung, and Blood Institute guidance as add-on treatment options for patients with severe asthma whose symptoms are not controlled by current optimized inhaled therapy (which usually involves the addition of long-acting muscarinic antagonist treatment to medium- or high-dose maintenance inhaled corticosteroid-formoterol/long-acting bronchodilator agonist as a starting point).^{3,4} Several of these therapies have been shown to enable the reduction of OCS use in both randomized controlled trials and real-world settings,^{16-18,20-25} with decreased mOCS dependence,^{5,24,26,27} and reductions in burst OCS use.^{20,22,24} Whereas the ambition is to eliminate OCS completely²⁸ (maintenance and burst, in accordance with a clinical remission outcome) when receiving biologic therapy, some patients still require OCS bursts for exacerbation control or are unable to discontinue mOCS therapy for asthmatic and non-asthmatic reasons.²⁹ Following the adage “prevention is better than cure,” there is a need to identify patients at risk of ongoing exacerbations through routine implementation of biomarker measurements in clinical practice. Biomarkers predicting responsiveness to biologics (eg, type 2 inflammation) can guide earlier intervention of biologics that may prevent at-risk patients from a cycle of exacerbations, recurrent OCS bursts, and escalation to mOCS, reducing the risk of future consequences such as lung function decline and airway remodeling, and thereby potentially effecting disease modification.³⁰⁻³³

Here, we describe the current prevalence of mOCS and OCS burst use, outline the related safety concerns and cumulative toxicity of OCS, and discuss strategies for reducing their use, including the potential role of biologics. The future focus of biologic therapy is moving beyond mOCS reduction to preventing escalation mOCS and minimizing OCS burst requirement. We offer expert opinion on implementing steps toward a future in which OCS burden is no longer a consideration for patients with asthma.

THE PROBLEM: HIGH PREVALENCE OF MAINTENANCE OR BURST OCS USE IN ASTHMA

Despite advancements in asthma treatment strategies and therapies, OCS use remains high. Managing this effectively requires understanding of patient history and medication patterns. However, quantifying the level of OCS use in patients is challenging owing to a lack of communication among health care professionals (HCPs) over previous OCS use and patient self-medication.

MAINTENANCE OCS USE

Currently, mOCS use varies by region,^{2,29,34,35} partly owing to differing access to specialist doctors and biologics. Estimates of the proportion of mOCS users range from 0.5% to 26.8% of patients with asthma based on a systematic literature review published in 2020.⁸ Even within a region, mOCS use can vary significantly between countries (eg, 21.4% of patients with severe asthma in Spain and 71.9% in Italy).³⁶ Evidence indicates that mOCS use has declined in recent years, as shown in a cross-sectional study of patients with severe asthma from the United States in the Optum database (2012–2022). The proportion of patients with asthma-related mOCS use was 4.9% to 5.0% in 2012 to 2017 and gradually declined to 4.5% in 2018 and 4.1% in 2022 (Figure 1).²⁷ Notably, this decline began even before biologics were widely available, likely reflecting heightened awareness of mOCS-related AEs. Most recently, a cross-sectional analysis of data from the UK-based Optimum Patient Care Research Database, which includes data from both before and after the licensure of biologics, found that the proportion of patients with severe asthma receiving a daily prednisolone-equivalent dose up to 15 mg has decreased steadily since the 1990s.⁵ Overall, the reduction in mOCS use aligns with the known OCS-sparing effects demonstrated in placebo-controlled trials and real-world studies of many biologics.^{16–18,20–25} However, mOCS use remains high in some areas,^{37,38} possibly as the result of limited access to biologics,¹⁴ suboptimal adherence to prescribing guidelines by physicians,³⁹ or the inability to stop OCS (eg, owing to withdrawal symptoms or adrenal insufficiency).^{40–42}

BURST OCS USE

Burst OCS use appears to have remained high over time, ranging from 46% to 93% of patients with asthma in one systematic literature review.⁸ Data from the US Optum study also indicate that burst OCS use remained high across calendar years 2012 to 2019 (about 35% of patients), followed by a drop to approximately 30% in 2020 to 2021 and a small increase in 2022 (Figure 1), potentially related to the COVID-19 pandemic.²⁷ The timing of these reductions aligns with the availability of biologic therapies such as mepolizumab, dupilumab, and benralizumab.⁵ The reductions in burst OCS use are notably lower than those observed in clinical studies of biologics in patients with severe asthma (which have indicated an approximately 50% reduction in exacerbations requiring OCS compared with control),⁴³ and also real-world clinical practice studies with these biologics, in which the rate of OCS bursts for exacerbations was reduced from baseline by 85% to 92% at 6 months,^{44,45} and 44% to 71% at 12 months.^{20,22,24} Although direct comparisons between the population-based study and real-world studies are challenging, because population-based studies typically include broader populations with potentially less severe patients compared with a real-world setting, the differences in OCS use reductions may reflect an issue of undermanagement, with some biologic-eligible patients not receiving full guideline-based treatment.⁴⁶ Together, these data indicate that exacerbations are not abolished, likely because some of these remaining exacerbations are of non–type 2 inflammation etiology.^{47–49} This highlights the importance of studies such as the MEX study,⁴⁸ which phenotyped remaining exacerbations in patients receiving

mepolizumab, and suggested that a proportion of residual exacerbations were driven by infection and would not benefit from OCS administration. The persistent real-world use of OCS burst may be also influenced by attempts to treat exacerbations of common comorbidities, such as flares of chronic rhinosinusitis with nasal polyps and asthma-chronic obstructive pulmonary disease overlap.^{3,50,51}

THE CONCERN: SAFETY

Long-term OCS use is associated with risk of adrenal insufficiency as well as metabolic, cardiovascular, ocular, psychiatric, and bone- and muscle-related complications, whereas acute OCS use increases the risk of infection, sepsis, thromboembolism, fracture, and gastrointestinal events.^{8,52–54} Importantly, evidence suggests that OCS toxicity is cumulative, and thus even a limited use of burst OCS can have long-term negative consequences.^{8,11,53} In a systematic review of AEs from systemic corticosteroids, a cumulative exposure of 0.5 to 1 g prednisolone equivalent (approximately 3–4 OCS bursts) increased the risk of osteoporosis as well as cardiovascular and cerebrovascular disease versus exposure of 0 to 0.5 g.¹¹ Similarly, in a series of 11 UK-based cohort analyses, most OCS-associated AEs were increased with a lifetime exposure of 0.5 g prednisolone equivalent compared with no exposure.⁹ Together, this highlights how all OCS use contributes to the overall OCS burden, regardless of whether it is prescribed as maintenance or burst therapy.

Taking into account the major safety risks of OCS use, an expert consensus framework proposed a definition of clinical asthma remission, as an ambitious treatment aim for patients on biologic therapy, which included the key criteria that biologic therapy should enable elimination of mOCS as a controller or burst OCS for exacerbations.²⁸ In a 2022 *Lancet* publication, clinical asthma remission was defined as a sustained absence of symptoms, exacerbations, and OCS use, along with stable lung function for a period of 12 months or more; this definition included remission on treatment, such as with biologic therapy.⁵⁵ In 2023, several national guidelines adopted clinical remission as a general treatment goal in asthma, with all definitions including no OCS use as an essential part of the remission criteria, a definition with which we agree.^{56,57} However, it appears that remission may be easier to attain for some patients than others. A retrospective analysis of the UK Severe Asthma Registry found that achievement of remission (defined as no OCS use, no significant symptoms, stable lung function, and patient and physician agreement that remission had been achieved) 1 year after biologic initiation was more likely in those with shorter asthma duration, older age when commencing biologic, and type 2 inflammation high endotype. Conversely, being female, being obese, having comorbid depression or anxiety, and having a high pre-biologic symptom burden were associated with decreased odds of achieving a clinical remission outcome³⁸ (notably, the presence of comorbidities may confound assessment of asthma-specific symptom control).⁵⁸ Additionally, a trend toward lower mOCS use at baseline was observed in patients achieving remission compared with those not achieving remission,³⁸ which was consistent with previous findings.^{59,60} Frequent OCS use is also associated with a failure to respond to biologic therapy.⁶¹ Together, these findings indicate that longer duration of disease, disease phenotype, and frequent OCS use before biologic initiation are

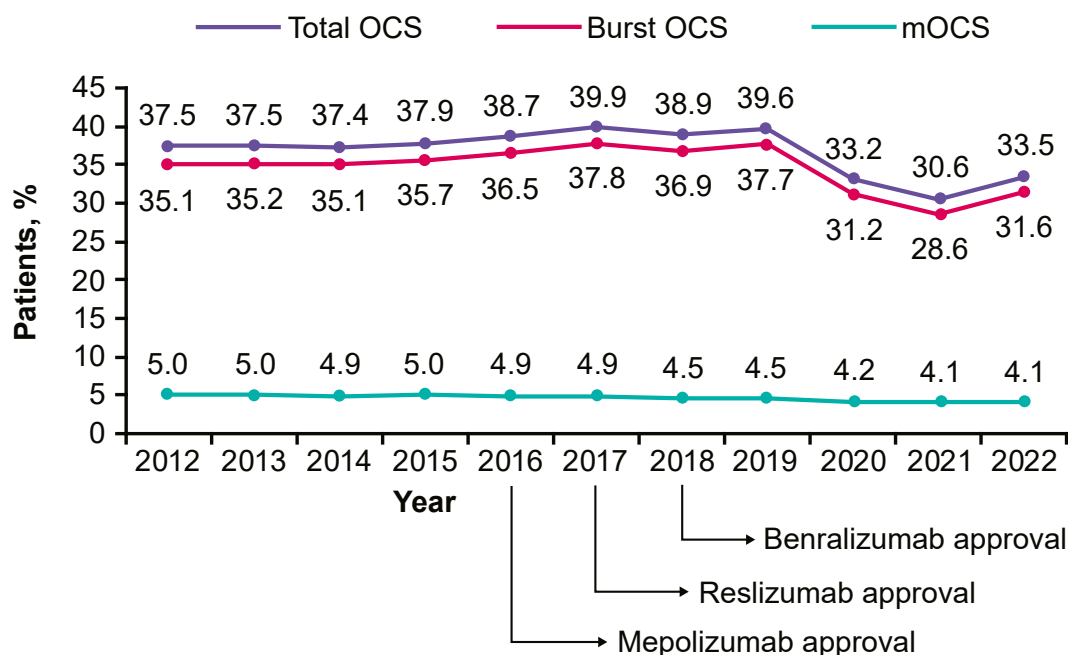


FIGURE 1. Proportion of patients receiving asthma-related maintenance oral corticosteroids (mOCS) and burst oral corticosteroids (OCS) in the United States. Figure reproduced with kind permission from Benson VS, et al.²⁷ Poster PA1175 presented at the ERS Congress, September 7-11, 2024, Vienna, Austria. Data are from the US Optum's deidentified Clinformatics Data Mart and represent patients with severe asthma before and after United States approval of the biologics mepolizumab (2016), reslizumab (2017), and benralizumab (2018). The period between 2020 and 2022 coincided with the global COVID-19 pandemic and subsequent lockdowns, which could have contributed to the reduction in asthma attacks and the use of burst OCS resulting from the decreased incidence of respiratory infections.

factors that decrease the likelihood of achieving remission after biologic initiation, emphasizing the need to limit OCS use through early optimization of therapy.

The need to minimize burst OCS and essentially eliminate mOCS use is supported by studies using the Glucocorticoid Toxicity Index (GTI), a clinical tool developed to measure change in glucocorticoid toxicity over time.⁶² Briefly, clinicians record data on key GTI domains (including blood pressure, glucose or lipid metabolism, bone mineral density, glucocorticoid myopathy, and skin toxicity). These data are then used to calculate two scores: the GTI Cumulative Worsening Score, which measures the total glucocorticoid toxicity since baseline (either permanent or transient), and the GTI Aggregate Improvement Score, which evaluates the effectiveness of a new therapy in reducing baseline glucocorticoid toxicity over time.⁶² In real-world patients, GTI-indicated toxicity correlated weakly with prednisolone dose, cumulative glucocorticoid toxicity, and the number of OCS bursts for exacerbations, but was more strongly correlated with asthma-related quality of life (QoL) measures, consistent with the significant impact of OCS exposure on patients' QoL. In the same patients, overall reductions in glucocorticoid toxicity after biologic therapy were observed, although these varied widely at the patient level, supporting the need to measure glucocorticoid toxicity directly.⁶² Further real-world evidence suggests that the degree of glucocorticoid toxicity was variable in patients, and 30% showed no improvement in toxicity (and displayed evidence of progressive toxicity 3 years later) despite a substantial reduction in OCS exposure.^{63,64}

This suggests that in some patients, OCS toxicity, when established, may not be fully reversible,^{63,64} underscoring the importance of minimizing lifetime OCS exposure, prioritizing early biologic intervention to prevent toxicity, and improving long-term outcomes (including an increased likelihood of clinical remission).⁶⁵

ECONOMIC BURDEN OF OCS USE

Oral corticosteroid use is frequently considered to be a low-cost option compared with other medications, but this does not take into account the potential harms caused by long-term OCS use.¹⁰ High OCS users (with ≥ 1 OCS fill with ≥ 30 days of supply or ≥ 6 OCS bursts/year) experience more hospitalizations and emergency department visits compared with low OCS users (with no OCS fills with ≥ 30 days of supply and maximum of 1 OCS burst/year) and consequently incur higher mean total annual health care costs (\$63,939 vs \$27,494, respectively).⁶⁶ Furthermore, costs increase in the presence of comorbidities. For instance, patients with both asthma and chronic obstructive pulmonary disease who are high OCS users have a mean total annual health care cost of \$80,580, compared with a mean total annual cost of \$40,933 in patients with asthma alone and high OCS use.⁶⁶ These figures are approximately halved in patients with low OCS use.⁶⁶ These findings underscore the importance to health care organizations of minimizing OCS use, particularly in long-term asthma management.

THE SOLUTION: MANAGING RISKS OF CUMULATIVE OCS BURDEN

Recent publications from international experts assessing the impact of OCS in asthma management, and international guidelines including GINA 2024, all agree that mOCS and burst OCS use should be reduced as soon as possible, wherever feasible.^{3,10,40,67-71} Although these recommendations reflect the shift over time in asthma management,³ there remains a need for more specific guidance on the maximum permissible OCS exposure and how to eliminate mOCS use and minimize burst OCS use. Beyond this, a holistic approach is required to ensure patients receive a correct and timely diagnosis, receive support for mood disorders that may influence asthma symptoms reporting, confirm that nonadherence (intentional or not) is not a factor, and that treatable traits (ie, specific, identifiable factors contributing to a patient's disease that can be modified through targeted interventions)⁷² are addressed.

In our opinion, it should be an aim of treatment that no patient is first administered mOCS or unnecessarily exposed to recurrent burst OCS. However, we acknowledge that barriers remain to achieving these goals. These include keeping track of OCS bursts prescribed by different HCPs; lack of access to resources such as asthma specialists, biomarker testing, and biologics; and an absence of reimbursement for biologic therapies in many countries. Furthermore, there is evidence suggesting that using a "symptom-based" treatment strategy leads to many symptomatic patients progressing to mOCS even though there is no evidence of underlying type 2 inflammation.^{37,73} A paradigm shift is needed as we move from a historic therapy to a newer horizon for patients with asthma, enabled by targeted therapy based on the four pillars of systems medicine: predictive, preventative, personalized, and participatory.⁷⁴

MAINTENANCE OCS

Although they all suggest mOCS use should be minimized, recommendations from international experts vary regarding how mOCS reduction should be achieved (Table I).^{2,67,70} Specific recommendations include using mOCS only at physiologic equivalent doses (ie, ≤ 5 mg/day)^{40,71} and using a threshold of 500 mg/year to trigger medication review.¹⁰ Global Initiative for Asthma 2024 recommends that mOCS (≤ 7.5 mg/day) should be used only as a last resort in adults with severe asthma if preferred therapies are not available or affordable.³ It is our opinion that a cumulative lifetime threshold dose of 500 mg should constitute an orange flag that triggers a medication review, with a lifetime threshold dose of 1 g constituting a red flag. We acknowledge that quantifying the level of OCS use in individual patients may be difficult in practice owing to a range of factors, and that individual susceptibility is a clinical reality, with potentially different side effects according to use in different diseases or target organs. Given the role of pharmacists in dispensing OCS, we suggest the involvement of pharmacists in designing both a national asthma action plan and an early warning system for patient exposure to OCS once it reaches this threshold.

BURST OCS

International experts also propose varying approaches to burst OCS use (Table I). Whereas some make no specific comment on burst use,^{40,70} others suggest that use should be minimized,^{67,69}

with specific suggestions for adult patients regarding the number (2/year triggering an HCP review), length (maximum of 7 to 15 days), and dose (0.5 mg/kg per day) of OCS bursts.^{2,10,71} Global Initiative for Asthma 2024 suggests OCS bursts of prednisolone at 40 to 50 mg/day for 5 to 7 days for treatment of a severe asthma attack in adults.³ There is also the possibility that OCS could be given only when there is evidence of a type 2 inflammation-driven exacerbation (raised FeNO [fraction of exhaled nitric oxide] or elevated blood eosinophils), whereas exacerbations without evident type 2 inflammation can be treated symptomatically without OCS.⁷⁵ Formal studies are needed to assess this approach. Because a significant proportion of asthma exacerbations are non-type 2,^{48,76} we believe this would better manage the use of OCS given as rescue bursts.

OCS TAPERING IN OCS-DEPENDENT SEVERE ASTHMA

Based on clinical findings,^{16-18,41,42} international experts recommend setting a target for an OCS end-dose, and careful monitoring for symptom control and adrenal insufficiency during dose reduction, particularly in patients with severe asthma who are receiving biologic therapies targeting type 2 inflammation (Table I).^{40,77}

The authors of this review have developed a set of recommendations regarding OCS use and tapering (Table II). These recommendations include a variable algorithm for OCS dosage reduction as first proposed in the PONENTE study⁴¹; briefly, suggestions for the extent and speed of OCS reduction are provided based on usage level (patients starting at >20 mg/day are advised to reduce by 5 mg/day per week; patients reaching 20 mg/day or starting at >10 to ≤ 20 mg/day are advised to reduce by 5 mg/day every 2 weeks, etc), with the largest and most rapid drops in OCS use occurring at the start of the tapering process.⁴¹ This flexible and patient-centered strategy enhances safety and effectiveness in achieving steroid reduction, aligning well with the goals of biologic therapy in asthma management.

THE ROLE OF BIOLOGICS

The development of biologics for asthma represents a fundamental shift in asthma management, in which clinical remission and eventual disease modification are now the ultimate goals.⁷⁸ Biologic therapies have been shown to be effective at reducing exacerbations, improving symptoms, QoL, and lung function in patients with severe asthma versus placebo.^{16-18,79-83} Biologic therapies targeting inflammatory pathways may improve the clinical symptoms of asthma and common comorbidities that share an underlying inflammatory signature.⁸⁴ Furthermore, because long-term safety data for biologics indicate that they are well-tolerated,⁸⁵⁻⁹⁰ the benefit-risk profile of biologics is more favorable than OCS.

Clinical or real-world studies have demonstrated reductions in OCS use with anti-IgE, anti-thymic stromal lymphopoietin, anti-IL4/13, and anti-IL-5 signaling biologics.^{16-18,20-25,41} Of these, key clinical studies of three different biologic therapies in severe asthma have demonstrated a reduction of mOCS versus placebo use as a key end point, including using specific OCS-tapering schedules,^{16-18,41} with relatively abrupt (reductions of 1.25-10 or 2.25-5 mg/day every 4 weeks) or more progressive (1.0-5.0 every 1-4 weeks) OCS withdrawal.^{16,17,41} Given the

TABLE I. Recommendation of international experts on OCS use and tapering

Publication	Publication type	OCS recommendation		
		mOCS	OCS bursts	mOCS tapering
Bakakos et al, 2022 ⁶²	Narrative review	Step-down mOCS dose after symptomatic control is gained after modification of contributory factors or better adherence is achieved	Dose should be tapered if given for >2 wk	None
Bleecker et al, 2022 ⁶⁷	Mini review and expert opinion	Use mOCS at lowest possible dose and taper as soon as possible	Only use SCS when clinically justified	None
Calzetta et al, 2021 ⁶⁸	Systematic review	As per GINA 2021 step 5: use low-dose mOCS	As per GINA 2021 step 4: use OCS bursts as initial controller with medium-dose maintenance inhaled corticosteroid/long-acting β_2 -agonist	None
Cataldo et al, 2021 ⁶⁹	Mini review and expert opinion	mOCS should not be considered first-line	OCS bursts should be avoided	OCS should be tapered to minimal dosage to maintain asthma control
Korn et al, 2022 ⁷⁷	Development of OCS-sparing methodology	None	None	OCS dose should be optimized before tapering, and a target dose established Patients should be monitored for symptom control and adrenal insufficiency
Lugogo et al, 2022 ⁷⁰	Expert opinion	mOCS should be avoided and biologics used earlier	None	There is a need for OCS tapering protocols
Gurnell et al, 2021 ⁴⁰	Narrative review	Daily mOCS should not exceed physiological equivalent doses (<5 mg/day)	None	None
Suehs et al, 2021 ⁷¹	Expert consensus	When mOCS is used, ≤ 5 mg/day is acceptable dose	OCS bursts should be given for a maximum of 5-7 days, with 0.5 mg/kg per day representing optimal dosage	OCS tapering should be attempted in patients with asthma control The speed of OCS tapering requires individualization
Haughney et al, 2023 ¹⁰	Expert consensus	>0.5 g prednisolone equivalent in 1 y should prompt HCP review	Two OCS burst courses in 1 y should prompt HCP review	None
GINA 2024 ³	International guidelines	As last resort, ≤ 7.5 mg/day	40-50 mg/day for 5-7 days	None

GINA, Global Initiative for Asthma; HCP, health care professional; mOCS, maintenance oral corticosteroid; OCS, oral corticosteroid; SCS, systemic corticosteroids.

decline in mOCS use since the introduction of biologic therapies, conducting clinical trials in patients who continue to be OCS-dependent (for reasons including adrenal insufficiency and the presence of comorbidities^{41,76}) is extremely challenging. Furthermore, with evidence currently available, there is no longer a need for formal OCS reduction studies with biologic approaches that have already been established as being beneficial in this respect.

Moreover, the earlier use of biologics might well be anticipated in reducing type 2 inflammation, to decrease severe exacerbation tendency, prevent progressive airway remodeling, and improve long-term patient outcomes, as well as preventing the negative impacts of either maintenance or burst OCS. This opinion is supported by studies such as GLITTER, a prospective cohort study using data from the International Severe Asthma

Registry.⁹¹ GLITTER indicated that biologic initiation in patients with severe asthma reduced exacerbations by approximately two thirds and that these patients were more likely to achieve mOCS dose reductions.⁹¹ With longer continuous therapy remission outcomes may improve even further, as suggested by a recent Italian study⁹² which reported that after 3 years of mepolizumab therapy, 73% of patients had achieved clinical remission (as reflected by no need for maintenance OCS, no need for rescue OCS bursts, good asthma control, and stabilization of lung function throughout the treatment period). Lower rates of clinical remission (30% to 38%, generally assessed at 12 months) were reported in a meta-analysis of 25 studies including patients with severe asthma who had been treated with biologics.⁶⁰ Although these outcomes are excellent, it is appreciated that a delay in initiating biologic therapy, with

TABLE II. Authors' recommendations on oral corticosteroid use and tapering

mOCS	Oral corticosteroid bursts	mOCS tapering
To be avoided	To be minimized	A variable dosage-reduction algorithm that includes rapid OCS tapering until reaching physiologic dosages (ie, 5 mg prednisone or prednisolone daily) followed by a personalized OCS reduction based on the degree of adrenal insufficiency ⁴¹
No patient to be initially given mOCS without being offered a biologic trial	Biomarker development for phenotyping of exacerbations in order to treat only when appropriate	
Comorbidities should be addressed		
Lifetime threshold dose of 500 mg: orange flag triggers a medication review		1. Starting at baseline prednisone/prednisolone dosage >20 mg/day Reduce by 5 mg/day every week When reaching 20 mg/day, proceed to step 2
Lifetime threshold dose of 1 g: red flag		2. Starting at baseline dosage >10 to ≤20 mg/day Reduce by 5 mg/day every 2 wk When reaching 10 mg/day, proceed to step 3
		3. Starting dosage >7.5 to ≤10 mg/day Reduce by 2.5 mg/day every 2 wk When reaching 7.5 mg/day, proceed to step 4
		4. Starting dosage >5 to ≤7.5 mg/day Reduce by 2.5 mg/day every 4 wk When reaching 5 mg/day for 4 wk, proceed to step 5
		5. At 5 mg/day for 4-wk morning cortisol (08:00-09:00 h) Normal: >350 nmol/L: continue down-titration (2.5 mg every 4 wk) Indeterminate (100-350 nmol/L): adrenocorticotropic hormone stimulation test (intravenous; 0 and 30 min): Normal (>450 nmol/L): continue down-titration (2.5 mg every 4 wk) Partial adrenal insufficiency (250-450 nmol/L): slow titration:(1 mg every 4 wk) and repeat test 2 mo later Complete adrenal insufficiency (<250 nmol/L): delay titration and repeat test 3 mo later Complete adrenal insufficiency (<100 nmol/L): delay titration and repeat test 3 mo later

mOCS, maintenance oral corticosteroid.

consequential recurrent OCS burden, may lead to consequences that are difficult to reverse, as suggested by a recent study in patients receiving mepolizumab for 12 months, which indicated that although glucocorticoid use decreased, this was not associated with a reduction in glucocorticoid toxicity.⁶⁴ This is directing thoughts toward the importance of earlier identification of patients and the initiation of biologics before glucocorticoid toxicity is established. Also, earlier intervention with biologics is in line with the statement “I deserve not to be reliant on oral/systemic corticosteroids,” which was proposed in a charter to improve patient care in asthma in 2018 and 2022, based on feedback from treaters and patient support groups.^{93,94}

Currently, we consider several barriers to physicians prescribing biologics over OCS. Biologics must be prescribed via specialty care after proper diagnosis and pheno-endotyping, as well as adherence checking and biologic counseling.⁹⁵ Although this is needed, not all patients will have access to a respiratory specialist, and not all respiratory physicians may feel comfortable prescribing biologics, resulting in underprescribing even among eligible patients. Additionally, not all patients are willing to receive injectable medications.⁹⁶ Furthermore, in low-income countries, biologics are often unavailable (or available only for short periods, making adherence challenging for all). Even in countries where biologics are accessible, strict reimbursement criteria further limit patient access.¹⁴ This is often compounded by OCS being inexpensive in the short term, with significant AEs

associated with OCS use being underrecognized.^{10,11} These risks, together with other barriers, can lead to primary care physicians (PCPs) defaulting to prescribing OCS. Raising awareness of these barriers is critical to facilitate early identification and timely referral of eligible patients for biologic therapy. Educating PCPs about the risk of OCS and the benefits of biologics, when appropriate, could encourage more proactive management, reduce time to referral, and improve patient outcomes.

The barriers highlight the importance of shared decision-making and the need for education for both patients and physicians about the cumulative risk of OCS use in accordance with the 2018 and 2022 charter to improve patient care in asthma.^{93,94} Patients have an integral role in deciding whether to initiate and continue biologic therapy. Patient satisfaction with therapy must be considered carefully, because decreased satisfaction will likely lead to reduced compliance. Moreover, patients may have different treatment goals than physicians and are less likely to accept lifestyle limitations.⁹⁷ They are therefore unlikely to have the same definition of remission as HCPs.

THE FUTURE: HOW CAN WE SHIFT CARE, MOVING FORWARD?

For decades, asthma exacerbations have been treated with OCS by PCPs, asthma specialists, and the patients themselves

using acute asthma action plans for self-management. In the current era, preventing exacerbations with early initiation of biologics and minimizing the need for OCS bursts is warranted, yet remain challenging. Before initiating a burst OCS for exacerbations, it may be beneficial first to determine the precise nature of the exacerbation, potentially using FeNO measurements and blood eosinophils to assess whether there is type 2 inflammation and whether OCS are needed. Anecdotal evidence is accumulating that those who are biomarker-low may recover with supportive therapy, in the absence of OCS intervention. Formal studies are needed to support this approach. However, data supporting these approaches are currently limited, and further research is needed to better establish when OCS use is appropriate. The contribution of multiple OCS bursts to overall cumulative OCS burden is underappreciated, including those routinely used to treat all types of exacerbation. Moreover, airway remodeling underlies these exacerbations, translating to irreversible lung function decline.^{31,32}

Reflecting previous proposals,⁹⁸ we suggest that both exacerbation risk and lifetime OCS burden need to be reduced. This could be accomplished by the earlier introduction of patient risk evaluation (ie, biomarker/predictive clinical trait identification) in asthma management, followed by prompt initiation of biologic therapies, allowing patients to benefit in terms of earlier disease control and preventing long-term impacts on lung function. The term “severe asthma” may be replaced in future with that of “patients at high risk” as a category of patients who may benefit from the use of biologics. Furthermore, after optimizing inhaled therapy, any patients who are already receiving mOCS or any patients with two or more exacerbations per year should be considered for a biologic trial. Thus, the definition of asthma exacerbation should be made more coherent among HCPs, and the need to prescribe OCS should be evaluated more carefully, especially in the absence of clinically significant respiratory distress such as shortness of breath and hypoxemia.

CONCLUSIONS

As early as 1958, patients with asthma with elevated sputum eosinophil counts were identified as most likely to benefit from OCS therapy. More than 60 years later, having progressed to the age of biologic therapies and the concept of clinical remission as a treatment goal, two questions must be addressed: (1) why are mOCS still used to treat patients with severe asthma, in whom biologics have been shown to be effective, including in reducing the frequency of acute exacerbations in type 2-high disease? and (2) why do we continue to tolerate repeated bursts of OCS when the cumulative consequences of such therapy have become clear? Additionally, with evidence suggesting that biologics may contribute to the reversal of airway remodeling, a benefit not observed with other interventions, there is a growing need to reevaluate the role of traditional OCS therapy.⁹⁹ Furthermore, as we consider more precision therapy, we might also ask whether we should try to phenotype exacerbations before resorting to burst OCS use. In other disease areas (eg, rheumatoid arthritis, ulcerative colitis) there has been a greater downward trend in OCS use over the past 2 decades,⁵ at least partly driven by a growing

understanding of the adverse impacts of OCS and the availability of biologics.^{100,101} In the context of asthma management, it is essential to follow their lead, raising our ambitions for patients.

It is time for the respiratory community to embrace a new age of corticosteroid stewardship for patient benefit, aiming to eliminate mOCS use and significantly reduce burst OCS use, initiating earlier use of biologic therapies and making high-risk patients a priority.

Acknowledgments

All authors contributed to the conception and interpretation of data for this review article in addition to reviewing it critically for important intellectual content and providing final approval of the version to be published. Editorial support in the form of writing assistance, including development of the initial draft from the author discussions, assembling tables and figures, collating authors' comments, grammatical editing and referencing, was provided by Hanna Mourad-Agha, PhD, at Fishawack Indicia Ltd, United Kingdom, part of Avalere Health, and was funded by GSK.

REFERENCES

1. Benedek TG. History of the development of corticosteroid therapy. *Clin Exp Rheumatol* 2011;29(5 suppl 68):S-5-12.
2. Bakakos P, Kostikas K, Loukides S, Makris M, Papadopoulos NG, Steiropoulos P, et al. Reducing tolerance for SABA and OCS towards the extreme ends of asthma severity. *J Pers Med* 2022;12:504.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2024. Updated May 2024. Accessed March 6, 2025. <https://www.ginasthma.org>
4. National Heart, Lung, and Blood Institute. 2020 focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217-70.
5. Menzies-Gow AN, Tran TN, Stanley B, Carter VA, Smolen JS, Bourdin A, et al. Trends in systemic glucocorticoid utilization in the United Kingdom from 1990 to 2019: a population-based, serial cross-sectional analysis. *Pragmat Obs Res* 2024;15:53-64.
6. Liang TZ, Chao JH. Inhaled corticosteroids. StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
7. Burrage WS, Irwin JW. The role of cortisone in the treatment of severe bronchial asthma. *N Engl J Med* 1953;248:679-82.
8. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020;201:276-93.
9. Bloechlinger M, Reinau D, Spoendlin J, Chang SC, Kuhlbusch K, Heaney LG, 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;19:75.
10. Haughney J, Winders T, Holmes S, Chanez P, Menzies-Gow A, Kocks J, et al. A charter to fundamentally change the role of oral corticosteroids in the management of asthma. *Adv Ther* 2023;40:2577-94.
11. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018;11:193-204.
12. Brown HM. Treatment of chronic asthma with prednisolone; significance of eosinophils in the sputum. *Lancet* 1958;2:1245-7.
13. Knowles JP. Difficulties in weaning in steroid treatment in asthma. *Br Med J* 1961;2:1396-9.
14. Porshjerg CM, Menzies-Gow AN, Tran TN, Murray RB, Unni B, Audrey Ang SL, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract* 2022;10:1202-16.e23.
15. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.

16. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
17. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448-58.
18. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475-85.
19. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med* 2022;386:157-71.
20. Blaiss M, Bleecker ER, Jacob-Nara J, Nair R, Duh MS, Wang Z, et al. Real-world effectiveness of dupilumab in patients with asthma: findings from the US ADVANTAGE study. *Ann Allergy Asthma Immunol* 2024;132:463-8.e1.
21. Braunstahl GJ, Chlumsky J, Peachey G, Chen CW. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy Asthma Clin Immunol* 2013;9:47.
22. Chung Y, Katial R, Mu F, Cook EE, Young J, Yang D, et al. Real-world effectiveness of benralizumab: results from the ZEPHYR 1 Study. *Ann Allergy Asthma Immunol* 2022;128:669-76.e6.
23. Hashimoto S, Kroes JA, Eger KA, Mau Asam PF, Hofstee HB, Bendien SA, et al. Real-world effectiveness of reslizumab in patients with severe eosinophilic asthma - first initiators and switchers. *J Allergy Clin Immunol Pract* 2022;10:2099-108.e6.
24. Pilette C, Canonica GW, Chaudhuri R, Chupp G, Lee FE, Lee JK, et al. REALITI-A study: real-world oral corticosteroid-sparing effect of mepolizumab in severe asthma. *J Allergy Clin Immunol Pract* 2022;10:2646-56.
25. Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S, Welte T, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. *Lancet Respir Med* 2022;10:650-60.
26. Graff S, Brusselle G, Hanon S, Sohy C, Dupont L, Peche R, et al. Anti-interleukin-5 therapy is associated with attenuated lung function decline in severe eosinophilic asthma patients from the Belgian Severe Asthma Registry. *J Allergy Clin Immunol Pract* 2022;10:467-77.
27. Benson VS, George M, Vichiendilokkul A. Has OCS use for severe asthma in the US decreased in the last 10 years? Poster PA1175 presented at the European Respiratory Society Congress; September 7-11, 2024. Vienna, Austria.
28. 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;145:757-65.
29. Chung LP, Upham JW, Bardin PG, Hew M. Rational oral corticosteroid use in adult severe asthma: a narrative review. *Respirology* 2020;25:161-72.
30. Busse WW, Melén E, Menzies-Gow AN. Holy Grail: the journey towards disease modification in asthma. *Eur Respir Rev* 2022;31:210183.
31. Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, et al. Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: results from SARP-3. *J Allergy Clin Immunol* 2021;148:752-62.
32. 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* 2023;78:643-52.
33. Tran TN, Heatley H, Rowell J, Chan JSK, Bourdin A, Chapaneri J, et al. Longitudinal patterns of intermittent oral corticosteroid therapy for asthma in the United Kingdom. *J Allergy Clin Immunol Glob* 2024;3:100225.
34. Dhar R, Rhee CK, Perng DW, Fukunaga K, Ip MS, Juthong S, et al. The burden of systemic corticosteroid use in asthma management in Asia. *Respirology* 2023;28:744-57.
35. Maspero JF, Cruz AA, Beltran CFP, Ali Munive A, Montero-Arias F, Hernandez Pliego R, et al. The use of systemic corticosteroids in asthma management in Latin American countries. *World Allergy Organ J* 2023;16:100760.
36. van Bragt J, Adcock IM, Bel EHD, Braunstahl GJ, Ten Brinke A, Busby J, et al. Characteristics and treatment regimens across ERS SHARP severe asthma registries. *Eur Respir J* 2020;55:1901163.
37. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. *Thorax* 2021;76:220-7.
38. McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. *Eur Respir J* 2023;62:2300819.
39. Mathioudakis AG, Tsilochristou O, Adcock IM, Bikov A, Bjerrum L, Cline E, et al. ERS/EAACI statement on adherence to international adult asthma guidelines. *Eur Respir Rev* 2021;30:210132.
40. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. *J Intern Med* 2021;290:240-56.
41. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med* 2022;10:47-58.
42. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Adrenal function recovery after durable oral corticosteroid sparing with benralizumab in the PONENTE study. *Eur Respir J* 2022;60:2103226.
43. Kyriakopoulos C, Gogali A, Markozannes G, Kostikas K. Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials. *Eur Respir Rev* 2024;33:230238.
44. Schleich F, Graff S, Nekoe H, Moermans C, Henket M, Sanchez C, et al. Real-world experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy* 2020;50:687-95.
45. Schleich F, Moermans C, Seidel L, Kempeneers C, Louis G, Rogister F, et al. Benralizumab in severe eosinophilic asthma in real life: confirmed effectiveness and contrasted effect on sputum eosinophilia versus exhaled nitric oxide fraction - PROMISE. *ERJ Open Res* 2023;9:00383-2023.
46. Charriot J, Maravic M, Huguet M, Vachier I, Suehs C, Bourdin A. "Real-life" management of patients with severe asthma in the biologics era: can we do better? *World Allergy Organ J* 2021;14:100528.
47. Huang D, Zhang L, Liu Y, Wang J, Zhang J, Baines KJ, et al. Activated non-neuronal cholinergic system correlates with non-type 2 inflammation and exacerbations in severe asthma. *Ann Allergy Asthma Immunol* 2024;133:64-72.e4.
48. McDowell PJ, Diver S, Yang F, Borg C, Busby J, Brown V, 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;9:1174-84.
49. Pincus AB, Fryer AD, Jacoby DB. Mini review: Neural mechanisms underlying airway hyperresponsiveness. *Neurosci Lett* 2021;751:135795.
50. Cazzola M, Rogliani P, Ora J, Calzetta L, Matera MG. Asthma and comorbidities: recent advances. *Pol Arch Intern Med* 2022;132:16250.
51. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020;58:1-464.
52. Brennan V, Martin-Grace J, Greene G, Heverin K, Mulvey C, McCartan T, et al. The contribution of oral and inhaled glucocorticoids to adrenal insufficiency in asthma. *J Allergy Clin Immunol Pract* 2022;10:2614-23.
53. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol* 2018;141:110-16.e7.
54. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415.
55. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. *Lancet Respir Med* 2024;12:96-9.
56. Majellano EC, Clark VL, Winter NA, Gibson PG, McDonald VM. Approaches to the assessment of severe asthma: barriers and strategies. *J Asthma Allergy* 2019;12:235-51.
57. Moermans C, Brion C, Bock G, Graff S, Gerday S, Nekoe H, et al. Sputum type 2 markers could predict remission in severe asthma treated with anti-IL-5. *Chest* 2023;163:1368-79.
58. Shackleford A, Heaney LG, Redmond C, McDowell PJ, Busby J. Clinical remission attainment, definitions, and correlates among patients with severe asthma treated with biologics: a systematic review and meta-analysis. *Lancet Respir Med* 2025;13:23-34.
59. Hansen S, Baastrup Søndergaard M, von Bülow A, Bjerrum AS, Schmid J, Rasmussen LM, et al. Clinical response and remission in patients with severe asthma treated with biologic therapies. *Chest* 2024;165:253-66.

62. Stone JH, McDowell PJ, Jayne DRW, Merkel PA, Robson J, Patel NJ, et al. The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum* 2022;55:152010.
63. McDowell PJ, Busby J, Stone JH, Butler CA, Heaney LG. Longitudinal assessment of glucocorticoid toxicity reduction in patients with severe asthma treated with biologic therapies. *J Allergy Clin Immunol Pract* 2025;13:298-07.e10.
64. McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Glucocorticoid toxicity reduction with mepolizumab using the Glucocorticoid Toxicity Index. *Eur Respir J* 2022;59:2100160.
65. Perez-de-Llano L, Scelo G, Tran TN, Le TT, Fageras M, Cosio BG, et al. Exploring definitions and predictors of severe asthma clinical remission after biologic treatment in adults. *Am J Respir Crit Care Med* 2024;210:869-80.
66. Broder MS, Raimundo K, Ngai KM, Chang E, Griffin NM, Heaney LG. Cost and health care utilization in patients with asthma and high oral corticosteroid use. *Ann Allergy Asthma Immunol* 2017;118:638-9.
67. Bleecker ER, Al-Ahmad M, Bjermer L, Caminati M, Canonica GW, Kaplan A, et al. Systemic corticosteroids in asthma: a call to action from World Allergy Organization and Respiratory Effectiveness Group. *World Allergy Organ J* 2022;15:100726.
68. Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Rogliani P, Chetta A. Oral corticosteroids dependence and biologic drugs in severe asthma: myths or facts? A systematic review of real-world evidence. *Int J Mol Sci* 2021;22:7132.
69. Cataldo D, Louis R, Michils A, Peche R, Pilette C, Schleich F, et al. Severe asthma: oral corticosteroid alternatives and the need for optimal referral pathways. *J Asthma* 2021;58:448-58.
70. Lugogo N, Mohan A. Are we poised to change the trajectory of maintenance oral corticosteroid use in severe asthma in the age of biologics? *Chest* 2022;162:4-5.
71. Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, et al. Expert consensus on the tapering of oral corticosteroids for the treatment of asthma. A Delphi study. *Am J Respir Crit Care Med* 2021;203:871-81.
72. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410-9.
73. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multi-centre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med* 2021;9:57-68.
74. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. *Per Med* 2013;10:565-76.
75. McDowell PJ, Busby J, Heaney LG. Asthma exacerbations in severe asthma: why systemic corticosteroids may not always be the best treatment option. *Curr Treat Options Allergy* 2023;10:53-63.
76. 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.
77. Korn S, Howarth P, Smith SG, Price RG, Yancey SW, Prazma CM, et al. Development of methodology for assessing steroid-tapering in clinical trials for biologics in asthma. *Respir Res* 2022;23:45.
78. Lommatzsch M, Virchow JC. Asthma remission: a call for a globally standardised definition. *Lancet Respir Med* 2025;13:2-3.
79. 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;3:355-66.
80. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017;5:390-400.
81. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573-82.
82. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
83. 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;384:1800-9.
84. Pavord ID, Bel EH, Bourdin A, Chan R, Han JK, Keene ON, et al. From DREAM to REALITI-A and beyond: mepolizumab for the treatment of eosinophil-driven diseases. *Allergy* 2022;77:778-97.
85. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019;143:1742-51.e7.
86. Korn S, Bourdin A, Chupp G, Cosio BG, Arbetter D, Shah M, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. *J Allergy Clin Immunol Pract* 2021;9:4381-92.e4.
87. Maspero JF, Peters AT, Chapman KR, Domingo C, Stewart J, Hardin M, et al. Long-term safety of dupilumab in patients with moderate-to-severe asthma: TRAVERSE continuation study. *J Allergy Clin Immunol Pract* 2024;12:991-97.e6.
88. Menzella F, Fontana M, Contoli M, Ruggiero P, Galeone C, Capobelli S, et al. Efficacy and safety of omalizumab treatment over a 16-year follow-up: when a clinical trial meets real-life. *J Asthma Allergy* 2022;15:505-15.
89. Menzies-Gow A, Wechsler ME, Brightling CE, Korn S, Corren J, Israel E, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. *Lancet Respir Med* 2023;11:425-38.
90. Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract* 2017;5:1572-81.e3.
91. Chen W, Tran TN, Sadatsafavi M, Murray R, Wong NCB, Ali N, et al. Impact of initiating biologics in patients with severe asthma on long-term oral corticosteroids or frequent rescue steroids (GLITTER): data from the International Severe Asthma Registry. *J Allergy Clin Immunol Pract* 2023;11:2732-47.
92. Bagnasc D, Bondi B, Caminati M, Nicola S, Pini L, Milanese M, et al. Evaluation of clinical remission in best-performing severe asthmatic patients treated for three years with mepolizumab. *Biomedicines* 2024;12:960.
93. Menzies-Gow A, Canonica GW, Winders TA, Correia de Sousa J, Upham JW, Fink-Wagner AH. A charter to improve patient care in severe asthma. *Adv Ther* 2018;35:1485-96.
94. Menzies-Gow A, Jackson DJ, Al-Ahmad M, Bleecker ER, Cosio Piqueras FBG, Brunton S, et al. A renewed charter: key principles to improve patient care in severe asthma. *Adv Ther* 2022;39:5307-26.
95. Clarke R, Burhan H, Joplin H, Arvanitis R, Bliss J. M30 Accelerating access to specialist care for asthma patients through innovative pathway transformation. *Thorax* 2023;78:A278-9.
96. Gleeson PK, Morales KH, Hvidas C, LaCava AF, Harhay MO, Rank MA, et al. Factors associated with asthma biologic prescribing and primary adherence among adults in a large health system. *J Allergy Clin Immunol Pract* 2023;11:1834-42.e4.
97. Canonica GW, Domingo C, Lavoie KL, Kaliaseithi A, Khan SQ, Majumdar A, et al. Asthma patients' and physicians' perspectives on the burden and management of asthma: post-hoc analysis of APPARENT 1 and 2 to assess predictors of treatment adherence. *Respir Med* 2024;227:107637.
98. Bardin PG, Price D, Chanez P, Humbert M, Bourdin A. Managing asthma in the era of biological therapies. *Lancet Respir Med* 2017;5:376-8.
99. Varricchi G, Ferri S, Pepys J, Poto R, Spadaro G, Nappi E, et al. Biologics and airway remodeling in severe asthma. *Allergy* 2022;77:3538-52.
100. Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology* 2021;160:2496-508.
101. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;114:384-413.