A Charter to Fundamentally Change the Role of Oral Corticosteroids in the Management of Asthma

John Haughney, Tonya Winders, Steve Holmes, Pascal Chanez, Andrew Menzies-Gow, Janwillem Kocks, Adel Mansur, Christopher Mcpherson, Giorgio Walter Canonica

Adv Ther (2023) 40:2577–2594
https://doi.org/10.1007/s12325-023-02479-0

REVIEW

A Charter to Fundamentally Change the Role of Oral Corticosteroids in the Management of Asthma

John Haughney · Tonya Winders · Steve Holmes · Pascal Chanez · Andrew Menzies-Gow · Janwillem Kocks · Adel H. Mansur · Christopher McPherson · Giorgio Walter Canonica

Received: November 8, 2022 / Accepted: February 21, 2023 / Published online: April 7, 2023

ABSTRACT

Asthma affects 339 million people worldwide, with an estimated 5–10% experiencing severe asthma. In emergency settings, oral corticosteroids (OCS) can be lifesaving, but acute and long-term treatment can produce clinically important adverse outcomes and increase the risk of mortality. Therefore, global guidelines recommend limiting the use of OCS. Despite the risks, research indicates that 40–60% of people with severe asthma are receiving or have received long-term OCS treatment. Although often perceived as a low-cost option, long-term OCS use can result in significant health impairments and costs owing to adverse outcomes and increased utilization of healthcare

J. Haughney (✉)
Glasgow Clinical Research Facility, Queen Elizabeth University Hospital, Glasgow, UK
e-mail: j.haughney@abdn.ac.uk

T. Winders
Allergy and Asthma Network, Vienna, VA, USA

T. Winders
Global Allergy and Airways Patient Platform, Vienna, Austria

S. Holmes
Park Medical Practice, Shepton Mallet, UK

P. Chanez
Department of Respiratory CIC Nord INSERM INRAE C2VN, Aix Marseille University, Marseille, France

A. Menzies-Gow
Royal Brompton and Harefield Hospitals, London, UK

J. Kocks
General Practitioners Research Institute, Groningen, The Netherlands

J. Kocks
Observational and Pragmatic Research Institute, Singapore, Singapore

J. Kocks
Groningen Research Institute Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

J. Kocks
Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

A. H. Mansur
Respiratory Medicine, Birmingham Heartlands Hospital and University of Birmingham, Birmingham, UK

C. McPherson
AstraZeneca, Cambridge, UK

G. W. Canonica
Department of Biomedical Sciences, Humanitas University, Milan, Italy

resources. Alternative treatment methods, such as biologics, may produce cost-saving benefits with a better safety profile. A comprehensive and concerted effort is necessary to tackle the continued reliance on OCS. Accordingly, a threshold for OCS use should be established to help identify patients at risk of OCS-related adverse outcomes. Receiving a total dose of more than 500 mg per year should trigger a review and specialist referral. Changes to national and local policies, following examples from other chronic diseases, will be crucial to achieving this goal. Globally, multiple barriers to change still exist, but specific steps have been identified to help clinicians reduce reliance on OCS. Implementing these changes will result in positive health outcomes for patients and social and economic benefits for societies.

Keywords: Asthma; Oral corticosteroids; Long-term

Key Summary Points

Approximately 40–60% of people with severe asthma receive long-term oral corticosteroids (OCS) treatment, which can result in adverse outcomes and increase healthcare costs long-term.

Frequent use of OCS for uncontrolled asthma should trigger an alert to identify when a referral to a specialist is needed.

Treatment focus needs to shift from short-term exacerbation management to better long-term control of the underlying disease.

A global reduction in the reliance on OCS can be achieved by establishing a threshold of 500 mg/year and implementing campaigns to raise awareness of the appropriate use of OCS.

G. W. Canonica
IRCCS Humanitas Research Hospital, Personalized Medicine, Asthma and Allergy, Milan, Italy

INTRODUCTION

Asthma affects approximately 339 million people worldwide [1], and this number is anticipated to grow by 100 million new cases by 2030 [2]. People with severe asthma, which is estimated to affect 5–10% of the total asthma population [3, 4], represent a distinct group of patients with asthma [3]. The disease seriously affects the lives of people with severe asthma. They experience more symptoms and exacerbations and a reduced health-related quality of life (HRQoL) compared with those with mild or moderate forms of asthma [5]. For these individuals, this can mean frequent, severe attacks; reductions in lung function; and a poor HRQoL [6, 7]. For example, these patients may encounter potentially debilitating adverse outcomes from long-term exposure to oral corticosteroids (OCS) [3, 6, 8]. OCS play a vital role in the management of asthma, particularly for acute exacerbations but also when treatment alternatives are not available or not considered appropriate [9].

Despite documented evidence of their short- and long-term adverse effects, OCS continue to be widely prescribed in patients with severe asthma worldwide. A study of medical records from 2011 to 2018 found that 14–44% of patients with asthma across four European countries were prescribed at least one OCS treatment during the 7-year study timeframe [10], and other research suggests as many as 61% of patients with severe asthma are currently receiving, or have received, long-term (chronic) OCS treatment [11].

Studies show there is variability between countries in rates of OCS prescriptions among patients with severe asthma [10, 12]. Perceived cost may be a reason for this variability; the relatively cheap up-front cost of OCS compared with other medications could be a factor in continued prescribing [13]. This trend may be driven by economic factors, expectations, differences among healthcare systems, and differences in education and guidance; however, that perception fails to consider larger economic and health effects.

OCS are essential and may be lifesaving in the management of acute severe asthma exacerbations [8]. However, many patients could have their treatments optimized to reduce the frequency of acute severe episodes, thereby reducing overall OCS exposure. The 2021 recommendations from the Global Initiative for Asthma (GINA) lay out a 5-step treatment guideline for patients with asthma based on their presenting symptoms [14], and evidence shows that OCS use increases with asthma severity. Among GINA steps 1–4, patients received a mean of 1.2 (step 1) to 2.0 (step 4) OCS courses per year, whereas those at step 5 received a mean of 5.3 courses [14]; and 20–60% of patients with severe asthma received long-term OCS, with the mean daily dosage range of 4–21 mg [8].

Frequent acute OCS use and long-term OCS therapy are both signals of uncontrolled asthma and should trigger a review to assess potential asthma triggers, patients' adherence to preventer medication, and their ability to use inhaler devices, as well as to evaluate the need for referral to an asthma specialist where the use of alternative, OCS-sparing treatments could be considered [15]. In many cases, however, the use of long-term OCS to control symptoms and exacerbations is accepted, often despite the availability of effective alternative treatments to improve symptoms and exacerbations without the adverse effects associated with OCS [8].

This charter seeks to reframe the complicated relationship that patients with asthma (and their healthcare professionals, HCPs) have with OCS. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

HEALTH AND ECONOMIC IMPACTS OF OCS USE

The significant adverse outcomes associated with acute and long-term use of OCS are well documented, and OCS-related adverse outcomes can have a significant impact on patient HRQoL [8, 9, 16, 17]. This can be particularly challenging for those with severe asthma because OCS have the potential to save their lives during acute episodes while also substantially impacting their longer-term HRQoL [18].

Cumulative, long-term use of OCS is associated with a greater risk of potentially debilitating adverse outcomes, including infection, bone- and muscle-related disorders, cardiovascular disease, ocular complications, chronic kidney disease, sleep disorders, and psychiatric disorders [8]. In one study, for example, OCS-induced morbidities were identified in 93% of patients with severe asthma [19]. Long-term use of OCS is also associated with increased mortality [20, 21]. A 2019 study estimated that the quality-adjusted life years lost from uncontrolled asthma were 752,230 in 2019 and are projected to increase to 783,474 by 2038 [22].

OCS-related adverse outcomes can also have negative economic impacts, as greater OCS exposure is associated with increased healthcare costs and healthcare resource utilization (HCRU) [8]. A 2020 study found that patients with severe refractory asthma on long-term OCS costed in excess of 40% more than those not on long-term corticosteroids because of the cost of medications and managing OCS-related adverse outcomes [9]. Furthermore, patients with high OCS use cost $17,122 (approximately €15,237) more annually than those with low OCS use [23], and those experiencing OCS-related adverse outcomes spend an average of $10,504 (approximately €9 348) more annually on all-cause healthcare [24].

OCS use also has substantial negative impacts on productivity. A 2021 study found that patients with asthma (79.2% of whom were OCS-dependent) missed an average of 15 working days and had reduced productivity at work, resulting in an average loss of €974 per patient per year [25]. Additionally, an observational prospective study found that 21% of patients with asthma reported their work was impaired, whereas patients receiving biologics reported a higher HRQoL than those receiving systemic corticosteroids [26]. Importantly, up to 47% of working-age patients seen in a severe asthma tertiary center were not employed [27].

Canadian studies found that lost workdays resulted in an estimated $78.1 to $94.4 million Canadian dollars (approximately €55 to €65

Table 1 Mean annual total healthcare costs by OCS use [8, 23, 32, 45]

	High OCS	Low OCS	No OCS	Difference high and low OCS	Difference high and no OCS
UK	£2603	£978	£560	£1625	£2043
Sweden	€5615	€2948	€1980	€2667	€3635
USA	$36,903	$19,780	—	$17,123	—
Germany	€11,253	€5096	€4266	$6157	€6987

OCS oral corticosteroids, *UK* United Kingdom, *USA* United States of America

million) of lost productivity annually in the city of Alberta, which has an asthma prevalence of 8.5% (total population of approximately 1.5 million working-age individuals) [28]. Furthermore, 50% of children with severe asthma missed 1–3 days of school per year [29]; thus, despite continued use of OCS, their asthma remained largely uncontrolled.

OCS use is associated with a significant increase in HCRU and costs for patients with asthma, with healthcare costs increasing with higher OCS exposure [8]. Analysis of a UK database found that non–asthma-related medication costs were 58% higher for those receiving long-term OCS versus those not receiving OCS owing to the need to manage OCS-related adverse outcomes [8]. Overall healthcare costs were 43% higher for OCS users than for nonusers and were also higher compared with patients with other chronic diseases, such as stroke, type 2 diabetes mellitus, chronic obstructive pulmonary disorder, and chronic kidney disease [8, 30]. A UK study by Kerkhof et al. that included 10,552 patients receiving long-term OCS therapy found comparable results, with a cost ratio 2.5 times higher for patients taking long-term OCS compared with all patients with asthma [31].

A study in Sweden also found a significant difference in total healthcare costs for those with long-term or periodic OCS compared to those with no OCS use [32]. Healthcare costs for patients with asthma and regular OCS use are an average of three times higher than for nonusers (no OCS use at €1980, low OCS use at €2948, and high OCS use at €5615; Table 1) [32]. This study also found that in-patient costs of OCS users were more than four times higher than for nonusers (€2329 versus €505) [32]. Additionally, an Italian study found that the cost per patient for OCS-related adverse outcomes were €285 or €892 higher for those with moderate or severe asthma, respectively, compared with control subjects without asthma [33]. This resulted in substantial budgetary impacts (Fig. 1).

A retrospective cohort study examined the long-term risks and associated costs for asthma patients in the UK taking systemic corticosteroids (SCS; $N = 9413$) versus those not taking SCS ($N = 9413$) [34]. The study found that patients taking 2.5 mg SCS per day used twice as many healthcare resources as those not taking SCS, and exposure to doses of at least 7.5 mg/day resulted in 2.3–3.0 times greater HCRU from adverse outcomes [34].

These costs increased over time. In the first year, all-cause costs (excluding asthma) for patients taking SCS were 7% higher, increasing to 50% by year 5 and 110% after 15 years. The average annual costs for adverse outcomes and

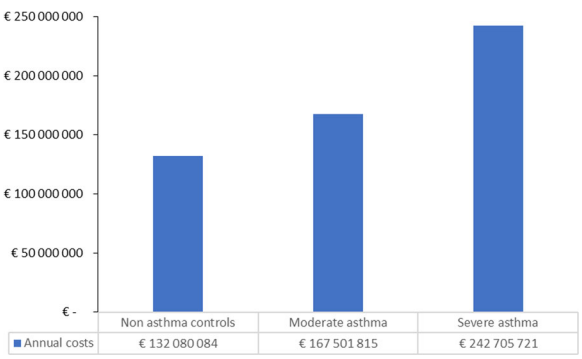

Fig. 1 Annual cost of OCS-related adverse outcomes [33]

asthma, respectively, were £1486 and £403 (approximately €1743 and €473) for SCS patients versus £1165 and £166 (approximately €1367 and €195) for non-SCS patients, representing a 42% higher cost expenditure [34]. Further analysis found a positive dose-dependent relationship between SCS exposure and annual costs, with a cost ratio of 1.25 for 0.5 to less than 2.5 mg/day, increasing up to 3.86 for 15 mg/day or more compared with non-SCS users. A similar cost pattern was also observed for acute vs long-term SCS exposure, with those with long-term exposure incurring higher costs [34].

Furthermore, high HCRU, particularly high rates of hospitalization, are also unsustainable. The coronavirus disease 2019 (COVID-19) pandemic exposed weaknesses in healthcare systems globally and especially highlighted the need for improved care for chronic airway diseases [35]. Care disruptions, such as those experienced throughout the pandemic, have significant consequences on patients' health. A study on the frequency of asthma exacerbation and HCRU found that patients with at least two exacerbations had more severe disease than those with at least one exacerbation. Total HCRU and asthma-related and all-cause hospitalizations were also higher for those at GINA step 5 versus step 1, with total asthma-related and all-cause costs per exacerbation increasing with disease severity [36].

With recent scientific advancements, targeted biologic treatments are now an option for many patients who were previously reliant on OCS [37]. Currently, six biologics are licensed for the management of asthma (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab), with approval and access to medications differing between countries [37–40]. However, despite the introduction of multiple biologic therapies, widespread acceptance and clinical use remain variable [41]. Although the up-front cost of these medications is higher than that of OCS, prolonged use of OCS has profound delayed health consequences, sometimes termed "shadow costs." The addition of corticosteroid-reducing therapies and subsequent reduction in OCS exposure have positive economic and health effects for patients [42].

A study of 106 Italian patients aged 18 years or more with uncontrolled asthma found that the addition of mepolizumab significantly reduced the number of corticosteroid-dependent subjects from 79.2% to 31.1% ($p < 0.0001$) and reduced the mean daily OCS consumption by 4.7 mg in those still dependent on OCS treatment ($p = 0.0002$) [25]. This study also found that mepolizumab reduced exacerbation rates (from 4.1 to 0.8; $p < 0.0001$) and hospital rates (from 0.4 predose to 0.06 postdose, $p < 0.0001$) [25].

This treatment also resulted in economic benefits. Patients prescribed mepolizumab missed significantly fewer workdays (15 days predose versus 4 days postdose, $p < 0.0001$), and fewer patients reported lost workdays (63.2% predose versus 31.2% postdose, $p < 0.0001$). Excluding the cost of the drug itself, the benefits of adding mepolizumab resulted in a total savings of €2469 per patient over 1 year of treatment, a relative reduction of 61.8% compared with pre-mepolizumab use—an economic return of around 22%, equivalent to the cost of 1 year of treatment with mepolizumab (€11,448). Therefore, it can be concluded that even though the annual drug cost of biologics is higher than that of OCS, treatment would result in long-term economic gains owing to reductions in comorbidities, hospital costs, and lost workdays [25].

A CHANGE IN OCS USE AND PRESCRIBING IS NECESSARY

Global clinical guidelines recommend limiting the use of OCS to manage asthma because of potentially serious adverse outcomes [3]. Despite this, the use of OCS is still relatively prevalent in all levels of asthma severity. Although OCS use differs across countries, it is notably widespread, as demonstrated by the international SABINA (SABA use IN Asthma) study on prescription patterns in asthma, which

found that over 1 year, OCS were used by 13% of patients in the general asthma population [43].

In 2018, a group of global experts and advocates developed a patient charter for people with severe asthma [3]. This charter laid out six core principles that patients with severe asthma should expect from their care. One of these principles stated that patients with severe asthma deserve to not be reliant on OCS [3]. In addition, a 2020 global template on quality standards for severe asthma care aimed at supporting improved access to and delivery of quality care also offered recommendations to support the reduction of OCS usage [44]. However, challenges remain with the day-to-day implementation of this goal worldwide. Because of a clinical legacy of limited alternative treatment options to OCS, there are often low expectations among patients and clinicians about the prospect of moving beyond OCS.

A comprehensive and concerted effort is necessary to tackle the issue of reliance on OCS. As with worldwide efforts to reform the usage of antibiotics, changing national and local policies will be crucial to ensure that OCS treatments become a last resort for patients with asthma. In some countries, such as Germany, localized guidelines on OCS prescribing are already in place [45].

In other disease areas, such as rheumatoid arthritis (RA), OCS use is declining [3]. RA affects nearly 2% of the population worldwide [46]. OCS were a common treatment for RA until biologics became available, despite a suggested link between treatment with OCS and mortality for patients with RA [47]. However, the advent of novel treatments, together with improved care, has led to a paradigm shift in treatment, relegating OCS to a "bridging" therapy, until the patient is transferred to a disease-modifying drug. Indeed, the probability of OCS use to treat RA has dropped from 55% (September 2001–March 2005) to 39% (March 2012–October 2015) [48]. This shift has involved earlier diagnoses, as well as earlier exploration of personalized treatment plans and alternative treatment options, such as biologics. Now is the time to act to ensure we achieve the same for patients with asthma.

Emerging evidence suggests that OCS use in the treatment of asthma is not reducing at the same pace [6]. In some countries, respiratory clinicians are the leading prescribers of OCS, accounting for as much as 40% of all OCS prescriptions [8]. Despite evidence of the significant adverse effects associated with OCS use, clinicians remain uncertain about the appropriate threshold at which to refer an individual with asthma to specialist care [49]. A step change is required to address the overreliance on OCS and ensure guidelines can be put into practice [50].

STEPS TO IMPLEMENT CHANGES WORLDWIDE

We must encourage clinical practice to move forward at the same pace as advances in science so that patients with asthma can access the best treatment at the right time. Although global guidelines for severe asthma exist to support the optimum approach to management and treatment [51], national policymakers must identify and implement tangible national strategies to improve respiratory care and adopt these best practices, such as reducing the use of OCS. The Global Quality Standard [44], which provides a "best practice" template to support improved access to and delivery of care, should help to support policymakers, HCPs, and patient advocacy groups to implement such strategies.

National and international strategies should be generated to allow new developments to reduce long-term OCS use, such as alternative treatments, available to all who could profit from such a therapy. The Severe Asthma Network in Italy stated in a 2020 publication that "considering the strong impact that frequent or regular use of OCS has on [the quality of life] of severe asthmatics, as well as the costs for managing corticosteroid-related disease, OCS-sparing up to withdrawal should be considered a primary outcome in the management of severe asthma" [52]. To address the overreliance on OCS, we have identified the following key headline actions, and a series of proposed measures, to address the barriers to change in OCS use (Table 2) [51, 53–56].

Table 2 Barriers to OCS prescription changes and steps to implement change

Barriers	Solutions	Steps to implement change	Recommended stakeholders to implement change
It is accepted that exacerbations are an unavoidable part of living with asthma	Implementing effective, balanced communication and information campaigns	Governments or other appropriate authorities should launch a multipronged campaign to raise awareness of the appropriate use of OCS to ensure people with asthma receive the right care at the right time	Government and PAGs
There is inconsistency in OCS usage dose and thresholds in asthma	Identifying the appropriate threshold for OCS usage	Articulating a threshold for OCS use that prompts action is essential to provide a goal that the healthcare community can work toward to improve patient outcomes and reduce inappropriate OCS use in severe asthma	Government and PAGs
Inappropriate reliance on rescue (reliever) medication can increase the OCS burden	Addressing the inappropriate use of rescue reliever medication	Patients should have an annual asthma review with their clinician	HCPs
		Patients should receive an asthma review when an alert flags them as having an ICS autorefill of < 80% per year [53, 56, 75]	HCPs and EMRs
		Patients should receive a structured treatment review when an alert flags SABA usage more than twice per week, as this indicates uncontrolled asthma and a medication adjustment is needed [51]. This should be embedded across healthcare systems as a trigger	HCPs and EMRs
		SABA monotherapy use should be discouraged and guidelines implemented to remove most SABA monotherapy from routine asthma management	HCPs, government, and PAGs
OCS are perceived as cheap and effective and are often preferred over inhalation devices	Challenging the perception that OCS are cost-effective	Prescription of > 500 mg prednisolone or equivalent in 1 year for adults, or two courses of acute treatment, should prompt review by a primary HCP or specialist. This process should be established within guidelines	Government and PAGs
		OCS-sparing asthma care strategies should be adopted whenever possible, using targeted treatments to minimize OCS use	HCPs, government, and PAGs
		Specific goals or targets for OCS reduction should be introduced across the healthcare system with incentives or monitoring to minimize the inappropriate systemic prescribing of OCS	HCPs and EMRs
		When there is no alternative and OCS are used, measures should be put in place to monitor patients for acute and chronic adverse outcomes	HCPs and EMRs

Table 2 continued

Barriers	Solutions	Steps to implement change	Recommended stakeholders to implement change
	Improving understanding and recognition of the OCS side effect profile	Patients should not be able to obtain repeat prescriptions of OCS without consultation with an asthma specialist	Government and HCPs
		Clinicians should receive consistent education on OCS use to ensure that all who prescribe OCS do so appropriately, beginning at medical school and reinforced during the professional life of all HCPs (e.g., ensuring correct diagnosis and need, as well as correct dosage for the relevant length of time)	Government and HCPs
		Education on the role of specialist assessment and new treatment options for all clinicians who treat respiratory diseases is essential (e.g., primary care, specialist care, emergency care, pharmacy) to help ensure that people with asthma are given the most appropriate treatment for their condition	HCPs and PAGs
		Updated guidance and resources on safe OCS prescribing should be widely available to all clinicians who treat respiratory diseases (e.g., primary care, specialist care, emergency care, pharmacy)	HCPs, government, and PAGs
		Adherence to long-term OCS should be measured using an objective test, e.g., the serum prednisolone/cortisol assay [54]	HCPs and EMRs
Fragmented systems broaden access to OCS and limit oversight	Ensuring systems have oversight and surveillance of OCS use	An infrastructure that enables real-time sharing of clinical data must be implemented, including alerts for OCS, SABA prescribing, and serious exacerbation events experienced by patients	HCPs and EMRs
		Alerts should be introduced to identify when a referral to specialist care or other appropriate action is needed (e.g., nonadherence, comorbidities, uncertainty of diagnosis, lack of asthma prescription autorefill, lack of asthma review after exacerbation)	HCPs and EMRs
		OCS use across different parts of the system should be monitored and action initiated either through an EMR or patient self-tracking (e.g., patient passport or app), depending on system capabilities, as a means of collecting clinical data points	HCPs and EMRs
		Two or more courses of OCS or > 500 mg prednisolone or equivalent (Table 3) should warrant an in-depth clinical review and referral (as per criteria outlined in the Global Quality Standard for Identification and Management of Severe Asthma [51])	
		Among HCPs, pharmacists are in a unique position to oversee patients' medication regimens that may come from numerous prescribers. As such, pharmacists should play a role, along with all HCPs, in identifying patients who have excessive OCS use and should discourage OCS dispensation without an HCP prescription	Pharmacists

EMR electronic medical record, *HCP* healthcare provider, *ICS* inhaled corticosteroids, *OCS* oral corticosteroids, *PAG* patient advocacy group, *SABA* short-acting beta agonists

Table 3 Corticosteroid equivalency table

	Equivalent dose, mg
Short-acting	
Hydrocortisone (cortisol)	20
Cortisone	25
Intermediate-acting	
Fludrocortisone	–
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Long-acting	
Dexamethasone	0.75

Acceptance that Exacerbations are an Unavoidable Part of Living with Asthma

Previous research has shown that avoidable risk factors contribute to premature death and suggest that past history is sometimes expected and/or accepted [57, 58]. This is evident from the percentage of patients with poorly controlled or uncontrolled disease who are treated in the primary care setting instead of by specialists [59].

Implementing Effective, Balanced Communication and Information Campaigns

Effective, balanced communication and information is needed to support HCPs and people with asthma in understanding how to use OCS appropriately. Much can be learned from other campaigns that involve surveillance and disease data monitoring, communications toolkits, and medical education and training [60].

Recommendation

Governments or other appropriate authorities should launch a multipronged campaign to raise awareness of the appropriate use of OCS to ensure people with asthma receive the right care at the right time.

Inconsistency in OCS Usage Dose and Thresholds in Asthma

Conflicting guidance on the OCS threshold that should trigger a specialist referral, in addition to a lack of consensus on an OCS threshold for treatment doses [49] and OCS tapering guidelines [61], contributes to confusion around the therapeutic approaches for patients with asthma.

Identifying the Appropriate Threshold for OCS Usage

Despite the evidence of the significant adverse outcomes associated with acute (short-burst) and long-term OCS use, uncertainty remains among clinicians regarding the appropriate threshold at which to refer an individual with asthma to specialist care. This uncertainty is fueled by multiple national guidelines, international strategies, and consensus documents for asthma, which present inconsistent—and, in some cases, conflicting—advice on the OCS threshold for specialist referrals [62]. Despite these inconsistencies, these guidelines also acknowledge that overuse of OCS puts patients at risk and therefore should be avoided when possible.

Recommendation

Articulating a threshold for OCS use that prompts action is essential to provide an aim/ambition that the healthcare community can work toward to improve patient outcomes and reduce inappropriate OCS use in asthma.

Inappropriate Reliance on Rescue (Reliever) Medication can Increase the OCS Burden

Evidence shows that long-term OCS use is most common in cohorts with high short-acting beta agonist (SABA) use [63]. HCPs recognize the OCS adverse effect profile, but the extent of use is not universally understood, nor perhaps is the opportunity for good preventative measures to reduce the need for acute OCS use in asthma (e.g., smoking cessation and use of inhaled corticosteroids, ICS) [51, 64]. Patient education

on the potential adverse effects of OCS use is lacking [65]. A lack of patient education also contributes to the overreliance on rescue medication because patients may not understand the difference between maintenance and rescue medications, and this can also lead to inadequate inhaler techniques [66].

Addressing the Inappropriate Use of Rescue (Reliever) Medication

As with high OCS use, overreliance on rescue inhalers is an effective indicator of uncontrolled asthma [51]. Studies have found that beta agonists can lead to worse asthma control due to bronchial hyperresponsiveness [8]. Evidence also demonstrates that rates of OCS prescriptions increase with increasing annual SABA refills and GINA step-therapy [67]. Consistent with efforts to reduce OCS use, GINA recommendations no longer advise SABA-only treatment in asthma [68]. Because of the link between high SABA use and OCS prescribing [69, 70], addressing the factors driving the inappropriate use of SABA will be critical to reducing OCS usage.

Focusing on exacerbations that require OCS use is just one measurement of asthma control [71, 72]. To better recognize the underlying factors contributing to OCS use, interrelationships among SABA reliance, symptom impairment, long-term adherence, and disease severity need to be understood in further detail. Policymaker action to limit SABA monotherapy use, ensure regular asthma reviews, and provide better post-exacerbation care is crucial not only in addressing SABA overreliance but also in tackling the overuse of OCS.

Recommendation

Patients should have an annual asthma review with their clinician. This may be determined by current local practice or guideline. One example is the recently developed ReferID [73, 74].

Recommendation

Patients should receive an asthma review when an alert flags them as having an ICS autorefill of less than 80% per year [53, 56, 75]. This alert may be from primary care (the prescriber) or a pharmacist (the dispenser). Some systems now allow automatic digital flagging through electronic means.

Recommendation

Patients should receive a structured treatment review when an alert flags SABA usage more than twice per week because this indicates uncontrolled asthma and a medication adjustment is needed [51]. This should be embedded across healthcare systems as a trigger.

Recommendation

SABA monotherapy use should be strongly discouraged and guidelines implemented to remove most SABA monotherapy from routine asthma management.

OCS are Perceived as Cheap and Effective and are Often Preferred over ICS Therapy

As a result of low acquisition costs for OCS, some payers and patients believe OCS are cost-effective for the healthcare system [33]. However, despite the low up-front costs, there are substantial indirect costs associated with the long-term use of OCS because of adverse effects and OCS-induced comorbidities, such as type 2 diabetes and obesity, and evidence suggests these long-term costs outweigh the up-front savings [24, 33].

Challenging the Perception that OCS are Cost-Effective

There is currently an incomplete understanding about OCS costs in healthcare. Payers perceive that OCS use in managing asthma is both cost-efficient for the healthcare system and effective for the patient [33]. With healthcare systems facing constrained budgets worldwide, the low acquisition costs of OCS [33] are often connected to positive short-term effects for the treated individual [9]. Although OCS may be correctly prescribed for acute exacerbations, this thinking does not account for the long-term costs of OCS use or the need to adjust treatment approaches for patients experiencing uncontrolled asthma.

OCS overexposure can lead to increased HCRU, poor outcomes, and greater cost per patient in the long term [33]. There will always be a need for clinicians to focus on the individual, some of whom have complex needs and situations. However, new therapies are emerging that may help to minimize exposure to OCS [9, 52]. National priorities should encourage clinicians to prescribe OCS as a well thought out option of last resort, rather than the status quo.

Recommendation
Prescription of more than 500 mg prednisolone (or equivalent), or two courses of acute treatment for adults with severe, uncontrolled asthma in 12 months should prompt review by a primary HCP or specialist. This process should be established within guidelines and reimbursement schemes.

Recommendation
There is a reluctance to implement consistent strategies for dosing or tapering. This view may explain why clinical behavior differs from the recommended clinical guidelines. OCS-sparing asthma care strategies should be adopted wherever possible, using targeted treatments to minimize OCS use.

Recommendation
Specific goals or targets for OCS reduction should be introduced across the healthcare system, with incentives or monitoring to minimize the inappropriate systemic prescribing of OCS.

Recommendation
When there is no alternative and OCS are used, measures should be put in place to monitor patients for acute and chronic adverse outcomes.

Improving Understanding and Recognition of the OCS Side Effect Profile Through Educational Campaigns

Although acute OCS treatment can be lifesaving in certain circumstances, use of OCS as a long-term treatment for asthma has become the status quo. At the same time, new treatment options—such as biologic treatments—remain underutilized in many parts of the world [8]. Since OCS use is commonplace across numerous care settings, it is not considered a "specialist" medicine that requires careful monitoring or consideration before being prescribed [76]. Relevant guidance and resources about safe OCS prescribing (including dosing and tapering) are not always widely available to the clinicians who prescribe them [36, 76]. As such, some clinicians may underestimate the side effects [77] and potential hazards of accumulated prescribing and long-term use of OCS [9, 42].

Whereas clinical education is of paramount importance, educating and empowering patients on the topic of OCS and its adverse outcomes are crucial. Some studies report that patients are satisfied with their OCS treatments but also report adverse outcomes [78]. Indeed, evidence from systematic reviews demonstrates that both acute and long-term OCS use are associated with an increased risk of acute and chronic adverse outcomes [8].

Recommendation
Patients should not be able to obtain repeat prescriptions of OCS without consultation with an asthma specialist, except where failure to do so would cause harm.

Recommendation
Beginning in medical school and reinforced during their professional life, all HCPs should receive consistent education on OCS use to ensure that those who prescribe OCS do so appropriately (e.g., ensuring correct diagnosis and need, as well as correct dosage for the relevant length of time).

Recommendation
Education on the role of specialist assessment and new treatment options for all clinicians who treat respiratory diseases (e.g., primary care, specialist care, emergency care, and pharmacy) are essential to help ensure that people with asthma are given the most appropriate treatment for their condition.

Recommendation
Updated guidance and resources on safe OCS prescribing should be widely available to all clinicians who treat respiratory diseases (e.g., primary care, specialist care, emergency care, and pharmacy).

Recommendation
When OCS tapering or withdrawal is being contemplated, adherence to long-term OCS should be measured using an objective test, e.g., the serum prednisolone/cortisol assay [54].

For those who are nonadherent to prescribed therapy, an alternative option should be employed (e.g., treatment optimization including potential escalation to biologic treatment).

Fragmented Healthcare Systems Broaden Access to OCS and Limit Oversight

A lack of evidence on acute and long-term OCS use in severe asthma exists because OCS prescribing occurs across a variety of care settings [10, 12].

Ensuring Systems Have Oversight and Surveillance of OCS Use

Across the healthcare system, systemic prescribing of OCS can occur in a variety of care settings, including general practice, urgent care clinics, specialist care (including respiratory; allergy; ear, nose, and throat), and pharmacy [10, 12]. There is often a lack of coordination and communication among these HCPs and settings (e.g., no single medical record), making it challenging to track OCS use [15].

In general, data and consistent recording of acute or long-term OCS usage in asthma are limited or incomplete [10, 12]. Risk measurement tools will be an important factor in addressing these issues by capturing the relevant data needed to trigger referrals to specialist care or take other appropriate action.

Recommendation
An infrastructure that enables real-time sharing of clinical data must be implemented, including alerts for OCS, SABA prescribing, and serious exacerbation events experienced by patients.

Recommendation
Alerts should be introduced to identify when a referral to specialist care or other appropriate action is needed (e.g., nonadherence, comorbidities, uncertainty of diagnosis, lack of asthma prescription autorefill, or lack of asthma review after exacerbation).

Recommendation
OCS use across different parts of the system should be monitored and action initiated either through an electronic medical record or patient self-tracking (e.g., a patient passport or app), depending on system capabilities, as a means of collecting clinical data points. In the UK, for example, the use of a steroid emergency card to support early recognition and treatment of adrenal crisis is promoted [79].

Better monitoring will enable clinicians across care settings to identify when a patient has reached the agreed threshold of long-term OCS use.

Recommendation
For adults, two or more courses of OCS or more than 500 mg prednisolone or equivalent in 1 year (Table 3) should warrant an in-depth clinical review and referral (as per criteria outlined in the Global Quality Standard for Identification and Management of Severe Asthma [44]).

Other techniques, such as promoting good medication adherence and addressing inhaler technique problems, should be considered after exacerbation.

Recommendation
Among HCPs, pharmacists are in a unique position to oversee patients' medication regimens that may come from numerous prescribers. As such, pharmacists should play a role, along with all HCPs, in identifying patients who have excessive OCS use and should discourage OCS dispensation without an HCP prescription.

CONCLUSION

Articulating a threshold for OCS use is an important step in communicating a goal that the community can work toward. It will help to identify a percentage of patients who would benefit from a transformation in care. During the COVID-19 pandemic, healthcare around the world faced catastrophic challenges and financial constraints [80]. The lessons from this pandemic have taught us the importance of enabling patients to have better long-term control of their conditions while building up healthcare resiliency and decreasing HCRU.

Evidence from other disease areas suggests that guideline changes are key drivers of change. For example, in RA, guidelines provide a specific maximum daily dose threshold for OCS use and advise tapering rapidly [47, 81]. The recommendations made here may need to be adapted on a country-by-country basis, depending on the availability of, and patients' access to, alternative medications based on country-specific approvals and cost.

However, defining a threshold is a complicated issue. In some individual cases, this threshold could be reached by the cumulative prescribing of OCS for more than one condition. The risk of OCS-related adverse outcomes is dose-dependent [8, 17].

The focus of asthma treatment needs to shift from short-term OCS use to manage exacerbations to a long-term outlook to better manage the underlying cause of the disease. This charter proposes a threshold for OCS use of 500 mg of OCS per year for adults with an ongoing condition. This threshold should be an indicator for action. An indication on a patient record of more than 500 mg over 12 months should trigger a medication review and specialist referral, once optimization measures in primary care have been exhausted. Available tools such as ReferID can also help identify patients in need of optimization [73, 74]. The FOCUS Working Group, a subgroup of the PRECISION program with a specific focus on OCS stewardship, agreed on the proposed threshold for OCS use, using existing literature to identify a threshold for action.

ACKNOWLEDGEMENTS

Funding. This manuscript, the Rapid Service Fee, and the Open Access Fee were funded by AstraZeneca (Gaithersburg, MD, USA).

Medical Writing, Editorial, and Other Assistance. Medical writing support was provided by Dorothy Keine, PhD, and Dan Jackson, PhD, CMPP, of CiTRUS Health Group (USA), which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Gaithersburg, Maryland, USA).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. John Haughney, Tonya Winders, Steve Holmes, Pascal Chanez, Andrew Menzies-Gow, Janwillem Kocks, Adel H. Mansur, Christopher McPherson and Giorgio Walter Canonica contributed to the manuscript conception and design, commented on previous versions of the manuscript, and read and approved the final manuscript.

Disclosures. John Haughney has consultancy agreements with AstraZeneca for the PRECISION program and has received consulting or speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, and Teva. Tonya Winders has received consulting and speaker fees from AstraZeneca, GlaxoSmithKline, Sanofi, Regeneron, ALK-Abelló, and Novartis. Steve Holmes has consultancy agreements with AstraZeneca for the PRECISION program and has received consulting or speaker fees from AstraZeneca, Beximco, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Johnson & Johnson, Mylan, Napp, Novartis, Nutricia, Orion, Pfizer, Sandoz, Teva, and Trudell Medical International. Pascal Chanez has consultancy agreements with AstraZeneca for the PRECISION program and has received research and

consulting funding from AstraZeneca, Almirall, Boehringer Ingelheim, Centocor, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Teva, Chiesi, and Schering-Plough. Andrew Menzies-Gow reports consultancy agreements with AstraZeneca and Sanofi; was an advisory board member for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Regeneron, and Teva; received speaker fees from AstraZeneca, Novartis, Teva, and Sanofi; has participated in research that his institution has been remunerated for from AstraZeneca and has attended international conferences sponsored by Teva. Janwillem Kocks reports grants, personal fees, and nonfinancial support from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline; reports grants and personal fees from Chiesi and Teva; reports grants from Mundi Pharma; has received personal fees from Merck Sharp & Dohme; has received personal fees from Covis Pharma outside of the submitted work; and holds 72.5% of shares in the General Practitioners Research Institute. Adel H. Mansur has received personal and institutional payments for talks and advisory board meetings, as well as grants from AstraZeneca, GlaxoSmithKline, Novartis, Teva, Sanofi, Boehringer Ingelheim, and Cheisi. Christopher McPherson is an employee of AstraZeneca. Giorgio Walter Canonica has previously received grant or research support from Boehringer Ingelheim, ALK-Abelló, and Stallergenes and honoraria or consultation fees from Menarini, GlaxoSmithKline, Sanofi, Teva, Hal, AstraZeneca, and Novartis.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Global Asthma Network. The Global Asthma Report. 2018. http://globalasthmareport.org/. Accessed 1 Nov 2022.

2. Enilari O, Sinha S. The global impact of asthma in adult populations. Ann Glob Health. 2019;85(1):2.

3. 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(10):1485–96.

4. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015;135(4):896–902.

5. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308–21.

6. Asthma UK. Severe asthma: the unmet need and the global challenge 2017. https://www.asthma.org.uk/1dcce9e9/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk_severeasthma_2017.pdf. Accessed 1 Nov 2022.

7. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. Eur Respir J. 2017;50(3):1700765.

8. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. Am J Respir Crit Care Med. 2020;201(3):276–93.

9. Chung LP, Upham JW, Bardin PG, Hew M. Rational oral corticosteroid use in adult severe asthma: a narrative review. Respirology. 2020;25(2):161–72.

10. Tran TN, King E, Sarkar R, et al. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. Eur Respir J. 2020;55(6):1902363.

11. Heffler E, Blasi F, Latorre M, et al. The severe asthma network in Italy: findings and perspectives. J Allergy Clin Immunol Pract. 2019;7(5):1462–8.

12. Tran TN, Maclachlan S, Hicks W, et al. Oral corticosteroid treatment patterns of patients in the United States with persistent asthma. J Allergy Clin Immunol Pract. 2021;9(1):338–46.e3.

13. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term systemic corticosteroid exposure: a systematic literature review. Clin Ther. 2017;39(11):2216–29.

14. Covvey JR, Johnston BF, Wood F, Boyter AC. Is the BTS/SIGN guideline confusing? A retrospective database analysis of asthma therapy. Prim Care Respir J. 2013;22(3):290–5.

15. Cataldo D, Louis R, Michils A, et al. Severe asthma: oral corticosteroid alternatives and the need for optimal referral pathways. J Asthma. 2020:58(4):448–58.

16. Papadopoulos NG, Barnes P, Canonica GW, et al. The evolving algorithm of biological selection in severe asthma. Allergy. 2020;75(7):1555–63.

17. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy. 2018;11:193–204.

18. Asthma and Allergy Network. Oral corticosteroid stewardship statement 2018. https://www.aafa.org/media/2244/oral-corticosteroid-stewardship-statement-november-2018.pdf. Accessed 1 Nov 2022.

19. Sweeney J, Patterson CC, Menzies-Gow A, 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.

20. Ekstrom M, Nwaru BI, Hasvold P, Wiklund F, Telg G, Janson C. Oral corticosteroid use, morbidity and mortality in asthma: a nationwide prospective cohort study in Sweden. Allergy. 2019;74(11):2181–90.

21. Lee H, Ryu J, Nam E, et al. Increased mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. Eur Respir J. 2019;54(5):1900804.

22. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The projected economic and health burden of uncontrolled asthma in the United States. Am J Respir Crit Care Med. 2019;200(9):1102–12.

23. Raimundo K, Ngai KM, Chang E, Broder M, Griffin NM. Cost and healthcare utilization in asthma patients with high oral corticosteroid-use. In: American Academy of Allergy, Asthma and Immunology annual meeting; March 4–7; Los Angeles, CA2016.

24. Luskin A, Antonova E, Broder M, Chang E, Omachi T, Ledford D. Health care resource use and costs associated with possible side effects of high oral corticosteroid use in asthma: a claims-based analysis. Clinicoecon Outcomes Res. 2016;8:641–8.

25. Bagnasco D, Povero M, Pradelli L, et al. Economic impact of mepolizumab in uncontrolled severe eosinophilic asthma, in real life. World Allergy Organ J. 2021;14(2):100509.

26. Soong W, Chipps BE, O'Quinn S, et al. Health-related quality of life and productivity among US patients with severe asthma. J Asthma Allergy. 2021;14:713–25.

27. Walters GI, Marsh J, Bahron A, Hussein H, Krishna MT, Mansur AH. Associations between employment and sociodemographic and health-related factors in asthmatic patients assessed at a regional severe asthma service. J Allergy Clin Immunol Pract. 2022;10:1646–8.

28. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. BMC Pulm Med. 2013;13:70.

29. Kohen DE. Asthma and school functioning. Health Rep. 2010;21(4):35–45.

30. O'Neill S, Sweeney J, Patterson CC, 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.

31. Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax. 2018;73(2):116–24.

32. Janson C, Lisspers K, Ställberg B, et al. Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids—a Swedish observational cohort study (PACEHR). Respir Res. 2018;19(1):168.

33. Canonica GW, Colombo GL, Bruno GM, et al. Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. World Allergy Organ J. 2019;12(1):100007.

34. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. Allergy. 2019;74(2):273–83.

35. Hurst J, Jenkins C, A M-G. A blueprint for change: how changes in chronic airways disease care can support the development of a more sustainable and resilient health system. AstraZenica. 2021. https://www3.weforum.org/docs/WEF_Blueprint_for_change_Chronic_airway_disease.pdf. Accessed 1 Nov 2022.

36. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. BMC Pulm Med. 2017;17(1):74.

37. The Asthma UK and British Lung Foundation Partnership. Biologic therapies for severe asthma 2020. https://www.asthma.org.uk/advice/severe-asthma/treating-severe-asthma/biologic-therapies/. Accessed 1 Nov 2022.

38. Agache I, Akdis CA, Akdis M, et al. EAACI biologicals guidelines—recommendations for severe asthma. Allergy. 2021;76(1):14–44.

39. Doroudchi A, Pathria M, Modena BD. Asthma biologics. Ann Allergy Asthma Immunol. 2020;124(1):44–56.

40. AstraZeneca. TEZSPIRE (tezepelumab-ekko) prescribing information. 2021. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/e306dc06-d580-4457-b15f-9f28545ad63a/e306dc06-d580-4457-b15f-9f28545ad63a_viewable_rendition__v.pdf. Accessed 1 Nov 2022.

41. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. J Allergy Clin Immunol Pract. 2022;10(5):1202-16.e23.

42. 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. Eur Respir J. 2018;52(4):1800703.

43. Quint JK, Arnetorp S, Kocks JWH, et al. Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. J Allergy Clin Immunol Pract. 2022;10(9)2297–2309.e10.

44. Haughney J, Winders TA, Holmes S, et al. Global quality standard for identification and management of severe asthma. Adv Ther. 2020;37(9):3645–59.

45. Taube C, Bramlage P, Hofer A, Anderson D. Prevalence of oral corticosteroid use in the German severe asthma population. ERJ Open Res. 2019;5(4):00092–2019.

46. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int. 2021;41(5):863–77.

47. Del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014;66(2):264–72.

48. Black RJ, Lester S, Buchbinder R, et al. Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. Arthritis Res Ther. 2017;19(1):253.

49. Price D, Bjermer L, Bergin DA, Martinez R. Asthma referrals: a key component of asthma management that needs to be addressed. J Asthma Allergy. 2017;10:209–23.

50. McCoul ED. Steroid shots and the culture of instant gratification. JAMA Otolaryngol Head Neck Surg. 2021;147(2):121–2.

51. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Accessed 1 Nov 2022.

52. Canonica GW, Blasi F, Paggiaro P, et al. Oral CorticoSteroid sparing with biologics in severe asthma: a remark of the Severe Asthma Network in Italy (SANI). World Allergy Org J. 2020;13(10): 100464.

53. Holmes J, Heaney LG. Measuring adherence to therapy in airways disease. Breathe. 2021;17(2):210037.

54. Mansur AH, Hassan M, Duffy J, Webster C. Development and clinical application of a prednisolone/cortisol assay to determine adherence to maintenance oral prednisolone in severe asthma. Chest. 2020;158(3):901–12.

55. Murphy KR, Chipps B, Beuther DA, Wise RA, McCann W, Gilbert I, et al. Development of the Asthma Impairment and Risk Questionnaire (AIRQ): a composite control measure. J Allergy Clin Immunol Pract. 2020;8(7):2263e5–74e5.

56. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–97.

57. Yang JF, Chaudhuri R, Thomson NC, et al. Insights into frequent asthma exacerbations from a primary care perspective and the implications of UK National Review of Asthma Deaths recommendations. NPJ Prim Care Respir Med. 2018;28(1):35.

58. Ryan D, Heatley H, Heaney LG, et al. Potential severe asthma hidden in UK primary care. J Allergy Clin Immunol Pract. 2021;9(4):1612–23.e9.

59. Royal College of Physicians. Why asthma still kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP [Internet]. 2014. https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills. Accessed 1 Nov 2022.

60. European Centre for Disease Prevention and Control. Antimicrobial resistance. 2020. https://www.ecdc.europa.eu/en/antimicrobial-resistance. Accessed 1 Nov 2022.

61. Boulet L-P, Godbout K. Oral corticosteroids tapering in severe asthma. Am J Respir Crit Care Med. 2021;203(7):795–6.

62. Drake SM, Simpson A, Fowler SJ. Asthma diagnosis: the changing face of guidelines. Pulm Ther. 2019;5(2):103–15.

63. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among Texas Medicaid patients with persistent asthma. J Manag Care Spec Pharm. 2015;21(12):1124–32.

64. British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN). British guideline on the management of asthma. 2019. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/. Accessed 1 Nov 2022.

65. Song W-J, Won H-K, Lee SY, et al. Patients' experiences of asthma exacerbation and management: a qualitative study of severe asthma. ERJ Open Res. 2021;7(2):00528–2020.

66. Amin S, Soliman M, McIvor A, Cave A, Cabrera C. Understanding patient perspectives on medication adherence in asthma: a targeted review of qualitative studies. Patient Prefer Adherence. 2020;14:541–51.

67. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55(4):1901872.

68. Reddel HK, Fitzgerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. Eur Respir J. 2019;53(6):1901046.

69. Kaplan A, Mitchell PD, Cave AJ, Gagnon R, Foran V, Ellis AK. Effective asthma management: is it time to let the AIR out of SABA? J Clin Med. 2020;9(4):921.

70. Baron AJ, Flokstra-De Blok BM, Kerstjens HA, et al. High use of SABAs is associated with higher exacerbation rate in Dutch patients with asthma. J Asthma Allergy. 2021;14:851–61.

71. Allen-Ramey FC, Nelsen LM, Leader JB, Mercer D, Kirchner HL, Jones JB. Electronic health record-based assessment of oral corticosteroid use in a population of primary care patients with asthma: an observational study. Allergy Asthma Clin Immunol. 2013;9(1):27.

72. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. J Allergy Clin Immunol. 2012;129(3):S1–8.

73. AstraZeneca. Astha Referral Identifier. 2023. https://www.asthmareferid.com/. Accessed 1 Nov 2022.

74. Beekman M, Hales J, Al-Ahmad M, Del Olmo R, Tan TL. Breaking the vicious circle-the Asthma Referral Identifier (ReferID) tool. NPJ Prim Care Respir Med. 2022;32(1):40.

75. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. Thorax. 2012;67(8):751–3.

76. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2020. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf. Accessed 1 Nov 2022.

77. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. NPJ Prim Care Respir Med. 2015;25(1):15026.

78. Jaffuel D, Fabry-Vendrand C, Darnal E, Wilczynski O, Pain E, Bourdin A. Perception of oral corticosteroids in adult patients with asthma in France. J Asthma. 2021;58(7):946–57.

79. NHS England. Steroid Emergency Card to support early recognition and treatment of adrenal crisis in adults. 2020 [updated March 2022]. https://www.england.nhs.uk/2020/08/steroid-emergency-card-to-support-early-recognition-and-treatment-of-adrenal-crisis-in-adults/. Accessed 1 Nov 2022.

80. Kaye AD, Okeagu CN, Pham AD, et al. Economic impact of COVID-19 pandemic on healthcare facilities and systems: international perspectives. Best Pract Res Clin Anaesthesiol. 2021;35(3): 293–306.

81. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685–99.