Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 170 (2020) 106045

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Review article

Use of corticosteroids in asthma and COPD patients with or without COVID-19

Syed Shahzad Hasan [a,*], Toby Capstick [b], Syed Tabish Razi Zaidi [c], Chia Siang Kow [d], Hamid A. Merchant [a]

[a] Department of Pharmacy, University of Huddersfield, Huddersfield, UK
[b] Leeds Teaching Hospitals NHS Trust, St. James's University Hospital, Leeds, UK
[c] School of Healthcare, University of Leeds, Leeds, UK
[d] School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia

ARTICLE INFO

Keywords:
Asthma
Chronic obstructive pulmonary disease
Coronavirus disease 2019
Inhaled corticosteroid
Oral corticosteroid

ABSTRACT

The potential detrimental effects of steroids on the immune system to fight viral infections had always been a concern for patients on long term steroids in chronic conditions. A recent warning from WHO on systemic corticosteroid use amid COVID-19 raised suspicion among public and healthcare professionals regarding the safety of steroid use during the SARS-CoV-2 pandemic. The corticosteroids (inhaled and oral) are commonly prescribed in the management of asthma and COPD patients and any unsolicited changes in medications use may lead to potentially severe exacerbations and may risk patient lives. This article provides a critical review of clinical evidence and offers a detailed discussion on the safety and efficacy of corticosteroids in asthma and COPD patients, both with and without COVID-19.

1. Background

The World Health Organisation (WHO) recently on 13th March 2020 recommended against the routine use of systemic corticosteroids in the clinical management of severe viral pneumonia if coronavirus disease 2019 (COVID-19) is suspected [1]. This is due to the lack of effectiveness of routine treatment with corticosteroids and the risk of potential harm as reported in previous literature for viral pneumonia outbreaks, including Severe Acute Respiratory Syndrome (SARS) [1,2]. In fact, the SARS-Coronavirus-2 (SARS-CoV-2) causing COVID-19 is closely related to SARS-CoV-1 that caused the previous SARS outbreak [3].

Since patients with asthma and chronic obstructive pulmonary disease (COPD) represent a group where the inhaled corticosteroid (ICS) or oral corticosteroid (OCS) are commonly prescribed, therefore the risk-benefit assessment of corticosteroid use in this group of patients with or without COVID-19 diagnosis is needed. The discussion that follows, segregated into two different groups of patients with regards to the use of corticosteroids amid current COVID-19 outbreak: (i) asthma and COPD patients who do not have COVID-19 as yet, and (ii) asthma and COPD patients who have COVID-19, and is based on clinical evidence and risk-benefit assessment amid COVID-19 pandemic.

1.1. Use of corticosteroids in asthma and COPD patients without COVID-19

Due to the recent warning from WHO on systemic corticosteroid use in COVID-19 associated viral pneumonia and the potentially detrimental effects of steroids on the immune system to combat viruses, there has been a general fear of contracting the virus among patients on inhaled and oral corticosteroids (ICS and OCS, respectively) with asthma and COPD. There have been reports that the use of ICS has been associated with a respiratory infection. A (Cochrane) systematic review of 43 randomised controlled trials of inhaled fluticasone (n = 21,247) and budesonide (n = 10,150) among COPD patients reported that ICS may increase the risk of non-fatal serious adverse pneumonia events (requiring hospital admission) by 62% (OR 1.62, 95% CI: 1.00–2.62) to 78% (OR 1.78, 95% CI: 1.50–2.12) compared to control but without an increase in mortality, and this appears to be a drug-specific phenomenon or the class effect [4].

More recently, there has also been a suggestion of an increased risk of upper respiratory tract infections (URTI) associated with ICS use in asthma. In a 2019 systematic review of 17 randomized controlled trials in asthmatic patients (n = 15,336), the risk of URTI was increased with

* Corresponding author. University of Huddersfield, Huddersfield, UK.
E-mail address: s.hasan@hud.ac.uk (S.S. Hasan).

https://doi.org/10.1016/j.rmed.2020.106045
Received 12 April 2020; Received in revised form 13 May 2020; Accepted 25 May 2020
Available online 26 May 2020

ICS use compared to no ICS use (odds ratio 1.24; 95% confidence interval 1.08 to 1.42) [5]. However, the meta-analysis showing an increased risk for respiratory infection associated with ICS use, are comparatively small in asthmatic patients and includes pooled estimates with wide confidence intervals in COPD patients, and therefore the association is relatively weak. In addition, pneumonia is common in people in COPD, with risk factors including older age, lower body mass index, more severe airflow limitation, greater COPD exacerbation rates, and low eosinophil counts [6].

The increased risk of respiratory infection with ICS may be due to impairment in innate immune responses with a reduction in neutrophil recruitment [7,8] and a delay in viral clearance in COPD patients [9]. Nonetheless, impairment in immune response was not replicated in a recent study among asthmatic patients on ICS [10]. It is, however, possible that the effect of ICS may vary depending on the type of respiratory infection and patient factors such as the severity of their respiratory condition as well as the physicochemical properties of ICS. Fluticasone has been observed to reside for a longer duration in airway lumen and mucus due to its poor solubility and permeability across the airway mucosa [11]. Conversely, budesonide with greater solubility traversed quickly through the airways [11]. The prolonged presence of fluticasone in airways maintains longer glucocorticoid receptor occupancy and thus a sustained anti-inflammatory and immunosuppressive effect, which may explain its higher potency and extended local immunosuppression relative to budesonide [12]. Indeed, a meta-analysis of seventeen trials [13] with 15,336 asthmatic subjects revealed an increased risk of upper respiratory tract infection with fluticasone (Peto odds ratio: 1.18; 95% confidence interval 1.02–1.38) but not budesonide. Similarly, a meta-analysis of 25 randomised controlled trials involving 49,982 COPD subjects [14] demonstrated an increased risk of pneumonia with fluticasone (relative risk: 1.84, 95% confidence interval 1.47–2.30) but not budesonide.

The data related to the overall or differential effects of ICS on COVID-19 is still lacking though a recent *in vitro* study (preprint) [15] suggested not only their safety but also a preventive effect from COVID-19. The study found that ciclesonide and mometasone blocked the replication of SARS-CoV-2 by targeting viral non-structural protein 15 (NSP-15). Similarly, another *in vitro* study [16] of budesonide and bronchodilators (glycopyrronium and formoterol) demonstrated inhibitory actions on the replication and cytokine production of coronavirus HCoV-229E in the human respiratory epithelial cells. Therefore, we have no reason to believe that there is a direct pathological relationship between ICS use and COVID-19.

Regarding the use of OCS, Fardet et al. (2016) examined the risk of infections in the UK for patients on OCS for at least 15 days in primary care for any indication including asthma and COPD, alongside other conditions such as rheumatoid arthritis, inflammatory bowel disease, polymyalgia rheumatica/giant cell arteritis, connective tissue disease, and cancer) [17]. The study reviewed an anonymised electronic medical data of more than 275,000 patients retrieved from The Health Improvement Network and found that overall, the patients receiving OCS were at five times greater risk of developing lower respiratory tract infection than the control (hazard ratio 5.84; 95% confidence interval 5.61–6.08). However, the retrospective study covering such disparate medical conditions may subject to confounding, since for instance, asthma or COPD itself was associated with an increased risk of serious respiratory infections. A 2017 Cochrane review found that corticosteroids reduced the mortality and morbidity in adults with severe pneumonia (bacterial and/or viral) and significantly improved clinical outcomes [18].

While we do not find any studies on the association between the use of ICS/OCS and the acquisition of COVID-19, some hints can be found from emerging epidemiological studies that reported an association between asthma/COPD and COVID-19. We anticipate that patients with asthma or COPD would be at increased risk of COVID-19 and experienced a more severe course of infection due to limited pulmonary reserves. Nevertheless, to our contrary, an under-representation of patients with asthma/COPD in COVID-19 is seen (about 1.5% reported in Chinese studies) [19,20] when compared to the estimates of asthma and COPD prevalence (estimated 6.9% in China) [21]. A similar trend in patients was observed with SARS [22,23] and the Middle East respiratory syndrome [24]. Therefore, the possible inhibitory effect of ICS on the replication of SARS-CoV-2 and other coronaviruses that may subsequently prevent ICS users from acquiring COVID-19 cannot be ruled out. Besides, the use of ICS may limit or improve symptoms of the disease where ICS users may not be symptomatic to seek testing or treatment. A case report from Japan [25] suggested a possible improvement in the course of disease with the use of ICS ciclesonide. It was shown that three COVID-19 patients requiring oxygen therapy were recovered after administration of inhaled ciclesonide, though it may be argued that patients may have improved even without inhaled ciclesonide due to the absence of a control group in the case report.

For asthma and COPD patients who do not have COVID-19 as yet, it is important to maintain good symptom control with usual therapy. This is to minimise the risk of an exacerbation and the associated need for hospital intervention, which could potentially increase the patients exposure to acquire COVID-19. Furthermore, poorly controlled asthma may lead to a more complicated disease course for those with COVID-19 infection. A 2013 systematic review and meta-analysis of seven randomised controlled trials found that discontinuing ICS (preventer) in people with stable asthma more than doubled the risk of asthma exacerbation (relative risk 2.35; 95% confidence interval 1.88 to 2.92) [26]. Therefore, the benefit of continuing ICS therapy based on the respective guidelines outweighs the suspected risk of respiratory infection.

Some asthmatic patients may, however, benefit from add-on non-steroidal preventer/controller inhalers which may potentially reduce the steroid load (corticosteroid-sparing effect), such as long-acting beta2-adrenoceptor agonists (LABAs), mast-cell stabilisers (cromoglycates) or non-steroidal anti-inflammatory agents (nedocromil). The efficacy of chronic LABAs as corticosteroid-sparing agents was examined in a (Cochrane) systematic review of 10 randomised trials comparing high-dose ICS versus combined low-dose ICS plus LABA in which the addition of a chronic LABA permitted 37–60% reduction of the ICS dose without deterioration of asthma control [27]. In another study in poorly controlled severe steroid dependant asthmatic patients (1600 μg/day inhaled beclomethasone dipropionate and $\geq$5 mg/day oral prednisolone), the inhaled sodium cromoglycate (16 mg/day) resulted in a mean reduction of 3.68 mg/day oral corticosteroids (95% CI 1.35, 5.95) plus a significant improvement in the lung function demonstrated by the peak expiratory flow measurements [28]. Another older study reported an addition of nedocromil among patients on high doses of ICS (beclomethasone 1000 or 2000 μg a day) resulted in a minor reduction in the dosage of corticosteroids compared with placebo [29]. This approach requires careful supervision and close monitoring by experienced clinicians in asthma management, and albeit the use of cromoglycates may not be a cost-effective strategy in the clinical practice of asthma, it may however potentially help to reduce the ICS dose and risks amid COVID-19 pandemic [30].

In contrast to asthma, the benefits of ICS in COPD patients are less clear and therefore should be avoided unless the patients are very symptomatic and are frequent exacerbators. Dual long-acting bronchodilator inhalers achieve greater reductions in exacerbation frequency compared to ICS plus long-acting beta2-agonist combination inhalers, with a lower risk of pneumonia [31]. There have been equivocal results regarding the consequences of withdrawing ICS in COPD patients. A meta-analysis in 2007 [32] investigated the impact of ICS withdrawal in COPD patients and reported no significant increase in the overall rate of exacerbation but a clinically important increased risk of severity in the observed exacerbations. Besides, the time to the first exacerbation was significantly shorter among COPD patients who discontinued ICS. In addition, the lung function (−30 ml of forced expiratory volume in 1 s) and the quality of life was significantly impaired after ICS withdrawal. A

recent study examined the effect of ICS withdrawal in the context of dual bronchodilator therapy found that the deterioration in lung function and an increase in exacerbation frequency was greatest among COPD patients with a blood eosinophil count ≥300 cells/μL at baseline, which suggests that a subset of COPD patients are likely to benefit from ICS therapy [33].

On the other hand, the minority of patients with severe allergic asthma who are receiving maintenance OCS should be titrated to the lowest possible dose sufficient to maintain symptoms. These patients should be supported with the corticosteroid-sparing effects of the biological drug, omalizumab [34], which could reduce the risk of adverse events from OCS use including increased risk of respiratory infection and thus a potential reduction in healthcare costs. Similarly, other biologicals such as mepolizumab [35] and benralizumab [36] have a corticosteroid-sparing effect and may be considered in patients with severe eosinophilic asthma receiving maintenance OCS. A trial of withdrawal of OCS may be considered after patients have been asymptomatic or stable for several months on OCS. Since OCS have no role in the daily treatment of COPD due to a lack of benefit, tapering should be considered for COPD patients receiving OCS. Other potential COPD therapies such as phosphodiesterase-4 inhibitors (roflumilast) or macrolide antibiotics (azithromycin) in former smokers, should be considered in cases where symptoms of COPD are poorly controlled [37].

In summary, the benefits of continuing ICS (or OCS) treatment, therefore, outweigh the uncertain risks in the context of COVID-19 pandemic, and hence major respiratory and health societies recommended against discontinuation of ICS (or OCS) in asthmatic patients [38–45]. For COPD patients, they have also urged to maintain their regular therapy which may include ICS, to maintain a good control of symptoms and preventing potential exacerbations (Table 1).

1.2. Use of corticosteroids in asthma and COPD patients with CoViD-19

Viral respiratory infections have been one of the most common exacerbation triggers in asthma and COPD patients [46,47]. This can be explained by their ability to induce proinflammatory cytokines, such as IL-1, IL-6, and IL-11, within airway epithelial cells [48]. While it is still not known if COVID-19 may trigger an exacerbation in asthmatic and COPD patients, the similar induction of pro-inflammatory cytokines (including IL-1 and IL-6) and subsequent lung inflammation in COVID-19 suggests that an exacerbation is likely in patients with asthma/COPD [49]. Therefore, the main goal of therapy in asthma and COPD patients with COVID-19 is to decrease the risk of exacerbation that could further compromise pulmonary reserve. In COVID-19 asthmatic patients, the ICS dose may be up-titrated up to 4x baseline if asthma worsens (as indicated by the peak expiratory flow monitoring). This is particularly important in poorly adherent patients on low dose ICS, as this may prevent severe exacerbations, and reduce the need for rescue OCS courses [50]. An alternative option for patients who use a combination of ICS/LABA (long-acting β-agonists such as formoterol) inhaler as single maintenance and reliever therapy (SMART) is to increase the as-needed dose when symptoms flare, which has found to reduce the risk of severe exacerbations requiring OCS by two-thirds compared with those receiving only inhaled short-acting bronchodilator (SABA) [51].

For COPD patients, more frequent use of SABA (short-acting β-agonists) is warranted when symptoms flare and titrated to response [37]. If an acute exacerbation of asthma and COPD in the context of COVID-19 does occur, there is no reason to believe that a different than usual approach should be adopted in home/clinic/inpatient management, and patients/clinicians should follow individualised asthma/COPD self-management plan which may include the use of short course of OCS, as delaying therapy may increase the risk of a life-threatening exacerbation [52]. Short-term use of OCS in both asthma [53,54] and COPD [55,56] exacerbations accelerates the resolution of exacerbations, prevents disease progression, early relapse after emergency treatment, and

Table 1
Recommendation on the use of inhaled and oral corticosteroids by major respiratory and health societies.

Society	Recommendation	Reference
Global Initiative for Asthma (GINA)	'People with asthma should continue all of their inhaled medication, including inhaled corticosteroids, as prescribed by their doctor.' 'In acute asthma attacks, patients should take a short course of oral corticosteroids if instructed in their asthma action plan or by their healthcare provider, to prevent serious consequences.' 'In rare cases, patients with severe asthma might require long-term treatment with oral corticosteroids (OCS) on top of their inhaled medication (s). This treatment should be continued in the lowest possible dose in these patients at risk of severe attacks/ exacerbations.'	[38]
Global Initiative for Obstructive Lung Disease (GOLD)	'GOLD is not aware of any scientific evidence to support that inhaled (or oral) corticosteroids should be avoided in patients with COPD during the COVID-19 epidemic.' 'COPD patients should maintain their regular therapy.'	[39]
European Lung Foundation	'Patients with asthma should never stop taking their preventer inhaler unless asked to do so by a medical professional. Stopping your steroid inhaler could put you at higher risk of complications with COVID-19 due to making your asthma worse.'	[40]
American Lung Association	'If you use inhaled corticosteroids or intranasal steroids, there's probably not a risk to developing a weakened immune system. If you use oral corticosteroids, there's a slight increase of a suppressed immune system. If you're in an asthma flare, your healthcare provider can help you decide which medications are the right choice to help you breathe. Do not stop or avoid taking your medication without discussing it with your healthcare provider.'	[41]
British Thoracic Society	'There is no evidence that inhaled steroids increase the risk of getting COVID-19 so please advise your patients to continue with all of their inhalers, including ICS and ICS/LABA combination inhalers.' 'If your patient develops symptoms and signs of an asthma exacerbation then they should follow their personalised asthma action plan and start a course of steroids if clinically indicated.' 'For patients on maintenance oral corticosteroids, they should continue to take them at their prescribed dose as stopping steroids suddenly can be harmful. It is worth reiterating the "sick day rules" and reminding patients that if they become unwell (for any other reason) they need to increase their steroid dose appropriately (usually doubled).'	[42]
The Primary Care Respiratory Society	'People with asthma must continue their preventive ICS according to current guidelines.' 'Oral corticosteroids should be used in people with asthma attacks according to current UK guidelines. There is no	[43]

(*continued on next page*)

Table 1 (*continued*)

Society	Recommendation	Reference
	evidence to suggest appropriate use of OCS in asthma attacks will cause a worse outcome if COVID 19 or similar viruses are suspected to be the trigger.'	
Asthma and Allergy Foundation of America	'Steroids are not a risk for people with asthma, so continue to take your medications as prescribed.'	[44]
National Institute for Health and Care Excellence (NICE)	'Recommends that patients should continue taking their regular inhaled and oral medicines, including corticosteroids, in line with their individualized self-management plan. This includes those with COVID-19 or suspected of having it.' 'If they develop symptoms of COVID-19, the guidance advises that patients should not start a short course of oral corticosteroids and/ or antibiotics.' 'Patients using non-invasive ventilation at home should be advised that, because these are potentially infectious aerosol-generating procedures, they should take appropriate precautions such as using equipment in a well-ventilated room and using it way from other family members if possible.'	[45]

reduces morbidity. The OCS therapy can be stopped abruptly as soon as symptoms have subsided, and lung function has been improved. However, patients should be reminded that a short course of OCS should not be self-initiated in the presence of COVID-19 symptoms such as fever, dry cough, or myalgia [45]. The approach detailed above, including the management of exacerbations, is also applicable for the severely/critically ill COVID-19 patients with asthma and COPD patients receiving emergency care in the hospital.

In a response to COVID-19 outbreak, the consultant endocrinologists/diabetologists advised considering a physiological stress dose of systemic corticosteroids (hydrocortisone 50–100 mg intravenously thrice daily) in hospitalised asthma and COPD patients (without exacerbation as yet) with chronic ICS/OCS use of longer than 3 months due to possible adrenal insufficiency [57]. Albeit, the use of systemic corticosteroids in the treatment of COVID-19 is discouraged by the WHO [1], we suggest that its use can be considered based on COVID-19 severity in COVID-19 patients with concomitant asthma or COPD. The use of systemic corticosteroids may not be justified for mild-to-moderate COVID-19 patients. In patients with severe/critical disease, especially those with septic shock or ARDS, where cytokine storm is increasingly being recognised, a systemic corticosteroid may play an important role. There are some retrospective studies [58,59] to support this at the moment, nevertheless, this will be confirmed soon from clinical trials and clinical experience from hospitalised COVID-19 patients in the current COVID-19 pandemic.

Inhaled corticosteroids are usually administered via an inhaler (such as a metered-dose inhaler or dry powder inhaler), but nebuliser solutions of corticosteroids are occasionally used in a clinical setting. Whilst joint guidance issued by The Department of Health, UK advised that administration of medication via nebulisation is not a viral droplet generating procedure, and so is not considered to represent a significant infectious risk [60], there are concerns from other sectors that this may not be the case. The World Health Organization, the Global Initiative for Asthma, and the UK's National Institute for Health and Care Excellence (NICE) have all advised that nebulised treatment can potentially increase the risk of virus transmission to healthcare personnel and other patients due to aerosolisation of SARS-CoV-2 [61,62]. Therefore, metered-dose inhalers with spacer devices should be preferred over nebulisers to deliver drugs wherever possible [61]. If nebulisation is inevitable, an airborne infection isolation room must be used for nebulisation with appropriate personal protective equipment and adequate contact and airborne precautions in place.

1.3. Key messages

The main goal of therapy for asthma/COPD patients with or without COVID-19 is to minimise the risk of an exacerbation. For patients without COVID-19, an exacerbation associated hospitalisation could potentially increase the exposure to acquiring COVID-19; and for patients with COVID-19, an exacerbation could further decrease pulmonary reserve. With this in mind, the clinicians should always consider the lowest possible ICS/OCS dose to maintain symptom control in patients with asthma to avoid the detrimental effects of corticosteroid therapy. Nevertheless, the use of ICS in patients with COPD is controversial, and for COPD patients on ICS who developed a frequent respiratory infection or are not responding to therapy, a reconsideration of management strategy is recommended on a case to case basis [7].

The management of an exacerbation of asthma and COPD in the context of COVID-19 pandemic should follow the usual approach, including the use of short courses of rescue OCS, while consideration for avoiding the use of nebulised drug administration should be made due to concerns about the transmission of COVID-19 in hospitalised patients unless nebulised in an airborne isolation room with necessary precautions. Studies are, however, lacking on the association between the use of ICS/OCS and the acquisition or severity of COVID-19. Future studies should, therefore, aim to collect data on the use of ICS/OCS in COVID-19 patients to ascertain the potential benefits or harms of ICS/OCS in COVID-19.

Declaration of competing interest

None.

References

[1] World Health Organization, Clinical Management of Severe Acute Respiratory Infection when CoViD-19 Is Suspected, World Health Organization, Geneva, 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. (Accessed 30 March 2020).
[2] C.D. Russell, J.E. Millar, J.K. Baillie, Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury, Lancet 395 (10223) (2020) 473–475.
[3] P. Zhou, X.L. Yang, X.G. Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[4] K.M. Kew, A. Seniukovich, Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. (3) (2014). Art. No.: CD010115.
[5] M. Yang, Y. Zhang, H. Chen, J. Lin, J. Zeng, Z. Xu, Inhaled corticosteroids and risk of upper respiratory tract infection in patients with asthma: a meta-analysis, Infection 47 (3) (2019) 377–385.
[6] H. Müllerova, C. Chigbo, G.W. Hagan, et al., The natural history of community-acquired pneumonia in COPD patients: a population database analysis, Respir. Med. 106 (8) (2012) 1124-1133.
[7] J.M. Davies, M.L. Carroll, H. Li, et al., Budesonide and formoterol reduce early innate anti-viral immune responses in vitro, PloS One 6 (11) (2011), e27898.
[8] J.L. Simpson, M. Carroll, I.A. Yang, et al., Reduced antiviral interferon production in poorly controlled asthma is associated with neutrophilic inflammation and high-dose inhaled corticosteroids, Chest 149 (3) (2016) 704-713.
[9] A. Singanayagam, N. Glanville, J.L. Girkin, et al., Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations, Nat. Commun. 9 (1) (2018) 2229.
[10] T. Southworth, C. Pattwell, N. Khan, et al., Increased type 2 inflammation post rhinovirus infection in patients with moderate asthma, Cytokine 125 (2020) 154857.
[11] M. Latorre, F. Novelli, B. Vagaggini, et al., Differences in the efficacy and safety among inhaled corticosteroids (ICS)/long-acting beta2-agonists (LABA) combinations in the treatment of chronic obstructive pulmonary disease (COPD): role of ICS, Pulm. Pharmacol. Therapeut. 30 (2015) 44-50.
[12] P.T. Daley-Yates, Inhaled corticosteroids dose regimens: therapeutic relevance of lipophilicity, solubility, dissolution and absorption from the lung, Am. J. Respir. Crit. Care Med. 201 (2020) A333.

[13] M. Yang, Y. Zhang, H. Chen, J. Lin, J. Zeng, Z. Xu, Inhaled corticosteroids and risk of upper respiratory tract infection in patients with asthma: a meta-analysis, Infection 47 (3) (2019) 377-385.

[14] M. Yang, Y. Du, H. Chen, D. Jiang, Z. Xu, Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials, Int. Immunopharm. 77 (2019) 105950.

[15] S. Matsuyama, M. Kawase, N. Nao, et al., The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15, bioRxiv (2020), 03.11.987016, https://doi.org/10.1101/2020.03.11.987016.

[16] M. Yamaya, H. Nishimura, X. Deng, et al., Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells, Respir Investig 58 (3) (2020) 155-168.

[17] L. Fardet, I. Petersen, I. Nazareth, Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study, PLoS Med. 13 (5) (2016), e1002024.

[18] A. Stern, K. Skalsky, T. Avni, E. Carrara, L. Leibovici, M. Paul, Corticosteroids for pneumonia, Cochrane Database Syst. Rev. 12 (12) (2017) CD007720.

[19] J. Yang, Y. Zheng, X. Gou, et al., Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis [published online ahead of print, 2020 Mar 12], Int. J. Infect. Dis. 94 (2020) 91-95.

[20] W.J. Guan, W.H. Liang, Y. Zhao, et al., Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis, Eur. Respir. J. (2020), 2000547 [published online ahead of print, 2020 Mar 26].

[21] GBD 2016 Occupational Chronic Respiratory Risk Factors Collaborators; GBD 2016 occupational chronic respiratory risk factors collaborators. Global and regional burden of chronic respiratory disease in 2016 arising from non-infectious airborne occupational exposures: a systematic analysis for the Global Burden of Disease Study 2016, Occup. Environ. Med. 77 (3) (2020) 142–150.

[22] C.Y. Chen, C.H. Lee, C.Y. Liu, J.H. Wang, L.M. Wang, R.P. Perng, Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome, J. Chin. Med. Assoc. 68 (1) (2005) 4–10.

[23] S.F. Ko, T.Y. Lee, C.C. Huang, et al., Severe acute respiratory syndrome: prognostic implications of chest radiographic findings in 52 patients, Radiology 233 (1) (2004) 173–181.

[24] F.Y. Alqahtani, F.S. Aleanizy, R. Ali El Hadi Mohamed, et al., Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study, Epidemiol. Infect. 147 (2018) 1–5 [published online ahead of print, 2018 Nov 5].

[25] K. Iwabuchi, K. Yoshie, Y. Kurakami, K. Takahashi, Y. Kato, T. Morishima, Three cases of the early to mid-stages of COVID-19 pneumonia improved by inhalation of ciclesonide, Available at: http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_200302_02.pdf. (Accessed 6 April 2020) https://writening.net/page?FC3QPm. and english translation at:.

[26] M.A. Rank, J.B. Hagan, M.A. Park, et al., The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials, J. Allergy Clin. Immunol. 131 (3) (2013) 724–729.

[27] P.G. Gibson, H. Powell, F. Ducharme, Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children, Cochrane Database Syst. Rev. 4 (2005) CD005076.

[28] H. Sakai, T. Shimoda, N. Matsuo, H. Matsuse, Y. Obase, S. Asai, S. Kohno, A. Edwards, Comparison of three treatment regimens of inhaled sodium cromoglycate in the management of adult patients with severe, steroid-dependent asthma, Ann. Allergy Asthma Immunol. 80 (6) (1998) 494–498. Jun, PubMed PMID: 9647273.

[29] C.S. Wong, S. Cooper, J.R. Britton, A.E. Tattersfield, Steroid sparing effect of nedocromil sodium in asthmatic patients on high doses of inhaled steroids, Clin. Exp. Allergy 23 (5) (1993) 370–376.

[30] F. Andersson, M. Kjellman, G. Forsberg, C. Möller, L. Arheden, Comparison of the cost-effectiveness of budesonide and sodium cromoglycate in the management of childhood asthma in everyday clinical practice, Ann. Allergy Asthma Immunol. 86 (5) (2001 May) 537–544.

[31] N. Horita, A. Goto, Y. Shibata, et al., Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD), Cochrane Database Syst. Rev. 2 (2) (2017). CD012066.

[32] L. Calzetta, M.G. Matera, F. Braido, et al., Withdrawal of inhaled corticosteroids in COPD: a meta-analysis, Pulm. Pharmacol. Therapeut. 45 (2017) 148–158.

[33] K.R. Chapman, J.R. Hurst, S.M. Frent, et al., Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (sunset): a randomized, double-blind, triple-dummy clinical trial, Am. J. Respir. Crit. Care Med. 198 (3) (2018) 329–339.

[34] G.W. Canonica, G.L. Colombo, P. Rogliani, et al., Omalizumab for severe allergic asthma treatment in Italy: a cost-effectiveness analysis from proxima study, Risk Manag. Healthc. Pol. 13 (2020) 43–53.

[35] E.H. Bel, S.E. Wenzel, P.J. Thompson, et al., Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma, N. Engl. J. Med. 371 (13) (2014) 1189–1197.

[36] P. Nair, S. Wenzel, K.F. Rabe, et al., Oral glucocorticoid-sparing effect of benralizumab in severe asthma, N. Engl. J. Med. 376 (25) (2017) 2448–2458.

[37] Global Initiative for Chronic Obstructive Lung Disease (Gold), Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2020 report, Available at: https://goldcopd.org/gold-reports/. (Accessed 30 March 2020).

[38] Global Initiative for Asthma (GINA), Recommendations for inhaled asthma controller medications, Available at: https://ginasthma.org/recommendations-for-inhaled-asthma-controller-medications/. (Accessed 30 March 2020).

[39] Global Initiative for Chronic Obstructive Lung Disease (Gold), GOLD CoViD-19 guidance, Available at: https://goldcopd.org/gold-covid-19-guidance/. (Accessed 30 March 2020).

[40] European Lung Foundation, Covid-19 – your questions answered by A respiratory expert, Available at: https://www.europeanlung.org/en/QA-covid-19. (Accessed 30 March 2020).

[41] American Lung Association, Asthma & COPD: CoViD-19 myth busting with Dr. Juanita Mora, Available at: https://www.lung.org/blog/covid-19-myth-busting. (Accessed 30 March 2020).

[42] British Thoracic Society, Advice for healthcare professionals treating people with asthma (adults) in relation to CoViD-19, Available at: https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-advice-for-healthcare-professionals-treating-patients-with-asthma/. (Accessed 30 March 2020).

[43] The primary care respiratory society. PCRS pragmatic guidance: Diagnosing and managing asthma attacks and people with COPD presenting in crisis during the UK Covid 19 epidemic, Available at: https://www.pcrs-uk.org/sites/pcrs-uk.org/files/resources/CoViD19/PCRS-Covid-19-Pragmatic-Guidance-v1-30-March-2020.pdf. (Accessed 30 March 2020).

[44] Asthma, Allergy Foundation of America, Coronavirus (CoViD-19): what people with asthma need to know, Available at: https://community.aafa.org/blog/coronavirus-2019-ncov-flu-what-people-with-asthma-need-to-know. (Accessed 30 March 2020).

[45] NICE Guideline, COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD), Available at: https://www.nice.org.uk/guidance/ng168/chapter/2-Treatment-and-care-planning. (Accessed 9 April 2020).

[46] D.J. Jackson, S.L. Johnston, The role of viruses in acute exacerbations of asthma, J. Allergy Clin. Immunol. 125 (6) (2010) 1178–1189.

[47] A. Mohan, S. Chandra, D. Agarwal, et al., Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review [published correction appears in Respirology. 2010 Jul,15(5):871], Respirology 15 (3) (2010) 536–542.

[48] D. Proud, C.W. Chow, Role of viral infections in asthma and chronic obstructive pulmonary disease, Am. J. Respir. Cell Mol. Biol. 35 (5) (2006) 513-518.

[49] P. Conti, G. Ronconi, A. Caraffa, et al., Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies [published online ahead of print, 2020 Mar 14], J. Biol. Regul. Homeost. Agents 34 (2) (2020) 1.

[50] T. McKeever, K. Mortimer, A. Wilson, et al., Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations, N. Engl. J. Med. 378 (10) (2018) 902–910.

[51] P.M. O'Byrne, J.M. FitzGerald, E.D. Bateman, et al., Inhaled combined budesonide-formoterol as needed in mild asthma, N. Engl. J. Med. 378 (20) (2018) 1865–1876.

[52] M.L. Edmonds, S.J. Milan, C.A. Camargo Jr., C.V. Pollack, B.H. Rowe, Early use of inhaled corticosteroids in the emergency department treatment of acute asthma, Cochrane Database Syst. Rev. 12 (12) (2012) CD002308.

[53] K.R. Chapman, P.R. Verbeek, J.G. White, A.S. Rebuck, Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma, N. Engl. J. Med. 324 (12) (1991) 788–794.

[54] B.H. Rowe, C.H. Spooner, F.M. Ducharme, J.A. Bretzlaff, G.W. Bota, Corticosteroids for preventing relapse following acute exacerbations of asthma, Cochrane Database Syst. Rev. 3 (2007) CD000195.

[55] D.E. Niewoehner, M.L. Erbland, R.H. Deupree, et al., Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group, N. Engl. J. Med. 340 (25) (1999) 1941–1947.

[56] I. Alía, M.A. de la Cal, A. Esteban, et al., Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support, Arch. Intern. Med. 171 (21) (2011) 1939–1946.

[57] U.B. Kaiser, R.G. Mirmira, P.M. Stewart, Our response to COVID-19 as endocrinologists and diabetologists, J. Clin. Endocrinol. Metab. 105 (5) (2020) dgaa148.

[58] C. Wu, X. Chen, Y. Cai, et al., Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online ahead of print, 2020 Mar 13], JAMA Intern Med. (2020), e200994.

[59] Y. Wang, W. Jiang, Q. He, et al., A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia, Signal Transduct Target Ther. 5 (1) (2020) 57.

[60] Department of health and social care (DHSC), public health wales (PHW), public health agency (PHA) northern Ireland, health protection scotland (HPS) and public health england. COVID-19: guidance for infection prevention and control in healthcare settings. As official guidance, Available at: https://www.fbu.org.uk/sites/default/files/attachments/Infection_prevention_and_control_guidance_for_pandemic_coronavirus.pdf. (Accessed 6 April 2020).

[61] Global Initiative for Asthma (GINA), COVID-19: GINA answers to frequently asked questions on asthma management, Available at: https://ginasthma.org/covid-19-gina-answers-to-frequently-asked-questions-on-asthma-management/. (Accessed 4 April 2020).

[62] W.H.O. Modes, Of transmission of virus causing coid-19, Available at: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. (Accessed 6 April 2020).