Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/8kky7827

ROLE OF INHALED CORTICOSTEROIDS VERSUS SYSTEMIC CORTICOSTEROIDS IN THE MANAGEMENT OF ASTHMA

Muhammad Hamad Khan[1*], Haroon Khan[2], Shafiq Ahmad[3], Muhammad Shahid[4], Aiza Ismail[5], Haseeb Haroon[6]

[1*]Student of Kabir Medical College, Gandhara University, Peshawar, KPK, Pakistan.
[2]MBBS, KABIR Medical College, Gandhara University, Peshawar, KPK, Pakistan.
[3]BDS, MPhil department of Pharmacology, Lecturer Pharmacology KMU, Institute of Dental Sciences, Kohat, KPK, Pakistan.
[4]MBBS, MPhil. Pharmacology, Institute of Pharmaceutical Sciences, Khyber Medical University, Peshawar, KPK, Pakistan.
[5]Student of Kabir Medical College, Gandhara University, Peshawar, KPK, Pakistan.
[6]BDS, MPhil. Scholar Pharmacology, Lecturer, Pharmacology Department, Kabir Medical College Gandhara University, Peshawar, KPK, Pakistan

***Corresponding author:** Muhammad Hamad Khan
*Email: hamadkhattak2367@gmail.com

ABSTRACT

Introduction: The aim of the current study was to analyze the comparison between the Inhaled Corticosteroids and Systemic Corticosteroids in the management of persistent asthma

Methods: In this study demographics analysis was conducted to examined the demographics characteristics of the participants. The descriptive analysis was conducted to examine the categorical variables. The difference between the lung functions test i.e., FEV1(Forced expiratory volume in the first second), FVC (Force vital capacity) and symptoms scores i.e., Asthma control test (ACT) between ICS(Inhaled corticosteroids) and SCS(systemic corticosteroid) groups was compared through t-test and chi-square test. While, multivariate analysis was used to examine the differences between the lung functions test i.e., FEV1, FVC and symptoms scores i.e., ACT between ICS and SCS groups when the potential cofounders were adjusted. Duration of asthma, severity, number of exacerbations in the past year, type of corticosteroid used (ICS or SCS), dosage, and duration of use, lung function tests (FEV1, FVC) and asthma control test (ACT) scores were analyzed through SPSS.

Results: The study found that after controlling for age, gender, BMI, and asthma duration, ICS was linked with significantly greater FEV1 compared to SCS (β coefficient = 0.28, p-value < 0.01). After adjusting for other covariates, the β coefficient for corticosteroid type (ICS vs. SCS) was 0.24, demonstrating a significant connection between ICS and greater FVC compared to SCS (p-value < 0.05). The β coefficient for corticosteroid type between ICS and SCS was 1.5, with a p-value < 0.01, indicating that patients on ICS had significantly higher ACT scores, indicating better asthma control. Longer asthma duration was a significant negative predictor (β = -0.2, p = 0.046), predicting poorer ACT scores. After controlling for relevant confounders, the multivariate analysis showed that ICS is linked with improved lung function (FEV1 and FVC) and asthma control (ACT scores) than SCS.

Conclusion: Exacerbations of persistent asthma are well treated with ICS. The best way to treat these individuals with ICS, how long they should take them for, and whether or not they should take systemic corticosteroids at the same time are all areas that need more investigation.

Keywords: Inhaled Corticosteroids (ICS), Systemic Corticosteroids (SCS), Asthma, Asthma Control Test(ACT)

Introduction

Persistent Asthma is a significant global healthcare issue. More than 27 million Americans have been diagnosed with asthma at some point, and around 1.8 million have had an attack in the last year and have gone to emergency room due to an asthma attack [1]. While adults are more likely to be affected by asthma than children, the disease nonetheless imposes a heavy burden on both demographics, and the financial toll is enormous. United States spent more than twelve billion dollars on asthma-related expenses. In Canada, the total cost surpassed $600 million, with 25% going towards the expense of acute asthma treatment, which includes trips to emergency rooms and hospitalizations [2].

Primary healthcare (PHC) institutions in Pakistan had a quarter of their patients with asthma, a serious respiratory condition [3]. In Pakistan, 4.3% of people have asthma, and 2.1% have chronic obstructive pulmonary disease (COPD). Among the several potential causes of a patient's visit to the emergency room, the most prevalent are environmental allergens, a superimposed infection of the upper respiratory tract, or inadequate management of long-term asthma [4, 5]. Due to the high risk of serious complications, anxiety for both patients and their parents, and even death, asthmatic emergency room visits are a defining moment for those living with the disease and their loved ones. Due to these reasons, a lot of work has gone into developing clinical practice and recommendations for the evaluation and management of acute asthma. Much work has been done on a national level to enhance and standardize asthma care, but there is still a long way to go before it catches up with what is really effective. The primary reasons for the variance are the different ways in which doctors diagnose asthma and the lack of consensus on how to manage this widespread condition [6].

Among the first successful treatment medicines for persistent asthma, corticosteroids (CS) were part of a number of early controlled clinical studies in the United Kingdom. There is a lot of study in this area now, and it may be confusing and even contradictory at times. A few definitions are in order before we can try to clear things up by reviewing the clinical literature [7]. Oral, intramuscular, or intravenous administration of corticosteroids are collectively referred to as "systemic corticosteroid" (SCS) throughout this discussion. SCS will be compared to 'inhaled corticosteroids' (ICS), which include corticosteroid medicine administered using a metered dosage inhaler, with or without a spacer, dry powder inhaler, or nebulizer. We should also mention that there has been a slow shift in the favored approach since inhaled agents came available [8]. When it comes to treating persistent asthma, ICS are now the go-to option, even if SCS were formerly the standard of care. [9].Some research has looked at the efficacy of inhaled corticosteroids for the management of persistent asthma attacks [10]. A systematic review analyzing eight randomized and blinded trials found that ICS are more effective than placebo in treating persistent exacerbation with elevated doses (>1 mg of budesonide and fluticasone) and to individuals going through severe persistent exacerbations [8, 11]. Results varied widely between trials because differences in asthma severity, ICS dose and frequency, and outcome variables such as admission rate, relapse rate, clinical signs and symptoms, pulmonary function, and oxygen saturation. Children who had recurrent viral wheezing and who began using high-dose fluticasone as (750 mcg BID) ten days prior to the onset of an infection of the upper respiratory tract required less rescue oral corticosteroids, according to another experiment [12].Several asthma recommendations, including GINA and EPR3, support the use of systemic corticosteroids for treating asthma exacerbations in the emergency department because of their overall effectiveness. They originally demonstrated a drop in the hospital admission rate But the findings of the five follow-up investigations were contradictory. No change in hospital admission rate or lung function was found after reviewing all six trials by Rodrigo and Rodrigo [13]. Nevertheless, it was only with systemic corticosteroids administered in medium or high dosages on lung function are more promising. While some trials found no impact of systemic corticosteroids on exacerbation recurrence after discharge. [14].Some research found that Inhaled corticosteroids (ICS) were more effective than systemic steroids in lowering admission rates, other studies found no difference between the two, while yet others found that ICS were more effective [15]. In a large-scale trial

including patients with mild to severe asthma, oral prednisolone resulted in a quicker improvement in forced expiratory volume in one second (FEV1) after 4 hours in the emergency department (ED) and a lower recurrence rate at 48 hours after discharge compared to systemic corticosteroids over the same time period. A recent study found that patients who were prescribed systemic corticosteroids and inhaled corticosteroids after leaving the emergency department experienced a rebound in their exhaled nitric oxide levels two weeks after leaving the hospital, even though they continued to take inhaled corticosteroids. Interestingly, neither the use of rescue medications nor FEV1 were affected by this rebound. The GINA guidelines state that inhaled corticosteroids (ICS) are effective for asthma exacerbations and can prevent relapses just as well as oral corticosteroids (OCS). On the other hand, the EPR3 guidelines suggest that high doses of ICS could be used in the emergency department (ED), but there is not enough evidence to say that it's better than oral systemic corticosteroids [16, 17].
Collectively, the current studies has a research gap of combined comparison of between Inhaled Corticosteroids and Systemic Corticosteroids for the treatment of asthma, therefore this study was conducted to analyze the comparison between the Inhaled Corticosteroids and Systemic Corticosteroids in the management of persistent asthma.

Study Objective

- To investigate the comparison between the effectiveness of ICS and SCS in managing persistent asthma in improving lung function.

Materials and Methods

The current study adopted a cross-sectional comparative research technique that allowed the collection of the data at a single point in the time and thus a snapshot of the status of the patients on ICS and SCS was collected. Ethical approval taken from ethical committee of hayat abad medical complex with approval number 2036 dated 7th august 2024.Patients visiting Hayatabad medical complex for treatment, diagnosed with the moderate to severe persistent asthma and taking the treatment of either ICS or SCS for at least six months. Below was the inclusion and exclusion criteria for the study.

Inclusion Criteria

- Patients having age from 18 to 65 years
- Diagnosed with moderate to the severe asthma
- Getting treatment of either ICS or SCS for at least 6 months

Exclusion Criteria

- Patients having other respiratory diseases
- Those patients who switched between SCS and ICS treatment

The sample size for the current study was analyzed through below formula

$$n = \frac{2(Z\alpha/2 + Z\beta)\sigma^2}{\Delta^2}$$

- Zα/2 is the critical value for a 95% confidence level =1.96)
- Zβ is the critical value for 80% power = 0.84).
- σ is the standard deviation of the outcome variable.
- Δ is the minimum detectable difference between groups.

$$n = \frac{2(1.96 + 0.84)10^2}{5^2}$$

$$n = 125.44 = 126$$

The number was rounded off to the nearest number to get 126 sample size. While for potential

dropouts, the sample size of 200 patients was considered and 100 patients each group (ICS and SCS) was taken. The sample was collected through convenient sampling technique and only those individuals were included who met the inclusion criteria. The data was collected through the structured questionnaire and the clinical assessment was conducted during single visit. The structured questionnaire consisted of Demographics i.e age, gender, BMI, Clinical History included Duration of Asthma: Measured in years and categorized into ranges (<1, 1-3, 4-6, 7-10, >10). Severity of Asthma: Measured as mild, moderate and severe. Number of Exacerbations in the Past Year: Recorded as the number of asthma exacerbations (none, 1-2, 3-4, 5-6, >6), Treatment Details included, Dosage: The dosage of the corticosteroid were recorded and Duration of Use: The length of time (in months) participants have been using their respective corticosteroid treatment. Lung function tests using spirometry which included FEV1 (Forced Expiratory Volume in 1 second) and FVC (Forced Vital Capacity) and Asthma Control Test (ACT) was used A validates questionnaire of ACT having 5 items was used to access the frequency of asthma, use of the rescue medications and control of asthma
In this study demographics analysis was conducted to examined the demographics characteristics of the participants. The descriptive analysis was conducted to examine the categorical variables. The difference between the lung functions test i.e., FEV1, FVC and symptoms scores i.e., ACT between ICS and SCS groups was compared through t-test and chi-square test. While, multivariate analysis was used to examine the differences between the lung functions test i.e., FEV1, FVC and symptoms scores i.e., ACT between ICS and SCS groups when the potential cofounders were adjusted. All the analysis were conducted through SPSS.

Results

Demographic analysis

Table1, as shown below, depicts comparison of results of the demographic analysis for the study.

Demographic Characteristic	ICS Group (n = 100)	SCS Group (n = 100)	p-value
Age (years)			
Mean (SD)	45.3 (12.4)	47.1 (11.7)	0.315
Age Categories			
18-30 years, n (%)	15 (15%)	12 (12%)	
31-45 years, n (%)	40 (40%)	35 (35%)	
46-60 years, n (%)	30 (30%)	33 (33%)	
61+ years, n (%)	15 (15%)	20 (20%)	
Gender			
Male, n (%)	40 (40%)	45 (45%)	
Female, n (%)	60 (60%)	55 (55%)	
Body Mass Index (BMI)			0.392
Mean (SD)	27.8 (4.3)	28.2 (4.1)	
BMI Categories			
Underweight (BMI < 18.5), n (%)	5 (5%)	4 (4%)	
Normal weight (BMI 18.5-24.9), n (%)	45 (45%)	43 (43%)	
Overweight (BMI 25-29.9), n (%)	35 (35%)	40 (40%)	
Obese (BMI ≥ 30), n (%)	15 (15%)	13 (13%)	

Table 1 showed that the mean age of participants in the ICS group was 45.3 years (SD = 12.4), while in the SCS group, it was 47.1 years (SD = 11.7). While the age categories showed the distribution of participants across different age ranges is relatively similar between the groups, with no significant differences (p-value = 0.315).
Similarly, the gender distribution in the ICS group was 40% male and 60% female, while in the SCS group, it was 45% male and 55% female. Likewise, the p-value of 0.543 indicated no significant

difference in gender distribution between the groups. Likewise, the mean BMI was 27.8 (SD = 4.3) in the ICS group and 28.2 (SD = 4.1) in the SCS group, while categorizing BMI into ranges showed a similar distribution between groups, with no significant differences observed (p-value = 0.392).

Clinical History

Below Table 2 showed the distribution across different categories of the clinical history of the study participants.

Table 2: Clinical History of Study Participants

Clinical History Characteristic	ICS Group (n = 100)	SCS Group (n = 100)	p-value
Duration of Asthma (years)			
<1 year, n (%)	10 (10%)	8 (8%)	0.721
1-3 years, n (%)	25 (25%)	22 (22%)	0.684
4-6 years, n (%)	30 (30%)	32 (32%)	0.830
7-10 years, n (%)	20 (20%)	24 (24%)	0.576
>10 years, n (%)	15 (15%)	14 (14%)	0.852
Severity of Asthma			0.564
Mild, n (%)	20 (20%)	22 (22%)	
Moderate, n (%)	50 (50%)	48 (48%)	
Severe, n (%)	30 (30%)	30 (30%)	
Number of Exacerbations in the Past Year			0.640
None, n (%)	40 (40%)	38 (38%)	
1-2, n (%)	30 (30%)	32 (32%)	
3-4, n (%)	20 (20%)	22 (22%)	
5-6, n (%)	7 (7%)	6 (6%)	0.821
>6, n (%)	3 (3%)	2 (2%)	0.751

The distribution of asthma duration in both groups is similar. For example, 10% of patients in the ICS group and 8% in the SCS group have asthma for less than 1 year. The p-values for each category indicated no significant difference in the duration of asthma between the two groups (p-value = 0.721).

The distribution of asthma severity is comparable between participants with 20% of patients in both groups classified as having mild asthma, 50% as moderate, and 30% as severe. The p-value of 0.564 indicated no significant difference in asthma severity among participants.

The number of exacerbations was also similar between participants. For instance, 40% of the ICS group and 38% of the SCS group experienced no exacerbations in the past year. The p-value of 0.640 shows no significant difference in the number of exacerbations between the two groups.

Overall, the clinical history showed that there was no significant difference between ICS and SCS group based on duration of the asthma, severity of asthma and number of the exacerbations in past year.

Multivariate Analysis

The multivariate analysis was conducted for the reason to isolate and then measure the independent effect of the corticosteroid type on the functions of the lungs and asthma control when the potential confounders were adjusted.

Table 3: Multivariate Analysis of Lung Function and Asthma Control Test Scores

Measure	β Coefficient (SE)	p-value
Adjusted Analysis of Lung Function		
FEV1 (L)		
Corticosteroid Type (ICS vs. SCS)	0.28 (0.08)	< 0.01
Age	-0.05 (0.03)	0.115
Gender (Male vs. Female)	0.10 (0.05)	0.053
BMI	-0.02 (0.01)	0.091
Asthma Duration (years)	-0.03 (0.02)	0.236
FVC (L)		
Corticosteroid Type (ICS vs. SCS)	0.24 (0.09)	< 0.05
Age	-0.06 (0.04)	0.080
Gender (Male vs. Female)	0.12 (0.06)	0.037
BMI	-0.01 (0.01)	0.277
Asthma Duration (years)	-0.04 (0.03)	0.161
Predictors of Asthma Control Test (ACT) Scores		
Corticosteroid Type (ICS vs. SCS)	1.5 (0.4)	< 0.01
Duration of Asthma (years)	-0.2 (0.1)	0.046
Age	0.1 (0.05)	0.053
Gender (Male vs. Female)	0.2 (0.3)	0.489
BMI	-0.05 (0.03)	0.101

a. FEV1 (Forced Expiratory Volume in 1 second)

The β coefficient for the type of corticosteroid (ICS vs. SCS) is 0.28 with a p-value < 0.01, indicating that after adjusting for age, gender, BMI, and asthma duration, ICS is associated with significantly higher FEV1 compared to SCS.

b. FVC (Forced Vital Capacity)

The β coefficient for corticosteroid type (ICS vs. SCS) is 0.24 with a p-value < 0.05, indicating a significant association of ICS with higher FVC compared to SCS after controlling for other factors.

c. ACT Scores

The β coefficient for corticosteroid type (ICS vs. SCS) is 1.5 with a p-value < 0.01, suggested that patients using ICS have significantly higher ACT scores, reflecting better asthma control compared to those using SCS. Similarly, Duration of asthma is a significant negative predictor (β = -0.2, p = 0.046), indicated that longer asthma duration is associated with lower ACT scores.

Thus, after adjusting the potential confounders, the multivariate analysis indicated that ICS is associated with better lung function (higher FEV1 and FVC) and better persistent asthma control (higher ACT scores) as compared to the SCS. Similarly, asthma duration also play significant roles in predicting lung function and asthma control.

Discussion

The current study investigated the comparison between the Inhaled Corticosteroids and Systemic Corticosteroids in the management of the asthma. The results indicated that after adjusting for confounding variables such as age, gender, BMI, and asthma duration, ICS was associated with significantly better lung function (higher FEV1 and FVC) and better asthma control (higher ACT scores) compared to SCS. Although the availability of some inhaled corticosteroids varies from country to country, these medications are now available for prescription for asthma patients [18]. There have been very few studies that have examined the efficacy of the different inhaled

corticosteroids; while doing so, it is essential to take into consideration the mode of administration as well as the kind of patient [10, 19]. It may be difficult to identify changes in the efficacy of inhaled corticosteroids owing to the fact that the dose-response curve for the clinical measurements that are often used for dosage comparisons is very flat [5]. In addition, while it has been difficult at times to ascertain the real clinical efficacy, the majority of comparisons have focused on differences in systemic effects at doses that are equally beneficial. Flunisolide, triamcinolone, budesonide are the only medications that are available in the United Kingdom, in contrast to the United States, where only BDP, budesonide are all that are available [20]. Patients suffering from asthma who are taking inhaled corticosteroids have not been the focus of a significant number of studies that compare doses. All patients who have symptoms that have persisted for an extended period of time should, from this point on, be provided inhaled corticosteroids as their first therapy. It is recommended that patients who need the use of a β2-agonist inhaler for the treatment of symptoms on a more frequent basis (or maybe three times per week) should start the process of inhaling corticosteroids. To effectively manage asthma, it is common practice to start with a modest dose of an inhaled corticosteroid and progressively increase the amount of medication being administered. Starting with a dose of 400 μg of corticosteroids, which falls within the middle of the recommended range, is the most effective method for managing asthma in a short amount of time, including the possibility that it will take some time [3, 16]. The dose of inhaled corticosteroid should be progressively lowered until it reaches the minimum quantity needed for optimal control. Once control is established, which is defined as normal or the greatest possible lung function, it is seldom necessary to utilize an inhaled β2-agonist. Considering that it may take up to three months for a response plateau to occur, it is recommended that you allow yourself at least that amount of time in between dose modifications. A strategy known as "start high - go low" is emphasized in the most recent recommendations that have been issued by the United States of America and the United Kingdom. When daily doses of 800 μg or more are necessary [18], it is advisable to use a high capacity spacer device in combination with a metered-dose inhaler and mouthwash with a dry powder inhaler. This is done with the intention of minimizing both local and systemic side effects. To achieve the highest possible level of adherence, inhaled corticosteroids are often administered twice day. When dealing with asthma that is more unstable, the suggested dosage is four times per day [16]. As far as budesonide is concerned, it seems that a once-day dosage is just as useful as a twice-daily therapy for persons who need around 400 micrograms or less on a daily basis. In the event that it is deemed necessary, the dosage of the inhaled corticosteroid should be increased to a daily dose of 2000 micrograms. However, since higher dosages have the potential to create systemic effects, it is possible that it may be more beneficial to take a modest dose of oral corticosteroids instead [17]. Inhaled corticosteroids, when administered in higher dosages, are not only expensive but also often induce unpleasant side effects in the region where they are applied [18, 19]. It has been claimed that nebulized budesonide might be used to increase the dose of inhaled corticosteroids while simultaneously reducing the need for oral corticosteroids. Despite this, this treatment technique is expensive and may primarily be successful owing to the fact that it is absorbed via the systemic system [20].

Conclusion

A lot of people suffer with asthma, and it can be a very crippling condition. In the sub-acute phase after an exacerbation, the therapeutic options outlined in this review that aim to manage bronchial inflammation provide promise for an early return to activities, reduced symptoms, and better quality of life. Acute asthma exacerbations are well treated with ICS. To better understand how ICS are used in these individuals, how long they should be taken for, and whether or not they should be used in conjunction with systemic corticosteroids, further study is urgently required. Furthermore, the safety of prescribing oral corticosteroids for home usage during an asthma attack requires further investigation.

Recommendations

The present research provides recommendations to physicians, urging them to make informed decisions about the corticosteroid therapy alternatives available to asthma patients. These decisions have the potential to result in management regimens that are more individualized and effective. In the same vein, the research suggested that by establishing the advantages of inhaled corticosteroids (ICS) over short-term corticosteroids (SCS) in terms of lung function and asthma control, the study supports the possibility for improved patient outcomes and better treatment of asthma symptoms, which ultimately leads to an improvement in the quality of life associated with asthma. The findings have an impact on the formulation and modification of clinical guidelines and treatment protocols for asthma management. These guidelines and protocols encourage the use of inhaled corticosteroids (ICS) in situations where it is deemed appropriate and ensure that treatment recommendations are in accordance with evidence-based practices.

Significance of the Study

Through a comparison of the efficacy of inhaled corticosteroids (ICS) and systemic corticosteroids (SCS), this study assisted both doctors and patients in making more informed choices about therapy. When seeking to assess the real impact that various forms of corticosteroid medication have on asthma, this research reminded practitioners of the significance of considering demographic aspects such as age, gender, and the length of time that they have been suffering with asthma into account. It is abundantly evident that larger, long-term studies are required in order to ascertain the effectiveness of these interventions across a wide range of patient demographics and settings, and the current study established the framework for future research.

Limitations of the study

The current study relied on cross sectional design for investigated which limited the ability of the researcher to establish a causal relationship. Similarly, the lack of the statistically significant differences in the primary variables suggest there is a need for the larger longitudinal studies for confirmation of the study findings. Similarly, in this study data was collected at a single point, however, the longitudinal studies can provide more detailed data for analysis.

References

1. Allen, D.B., *Inhaled corticosteroids and endocrine effects in childhood.* Endocrinology and Metabolism Clinics, 2020. **49**(4): p. 651-665.
2. Cardet, J.C., A. Papi, and H.K. Reddel, *"As-needed" inhaled corticosteroids for patients with asthma.* The Journal of Allergy and Clinical Immunology: In Practice, 2023. **11**(3): p. 726-734.
3. Haughney, J., et al., *A charter to fundamentally change the role of oral corticosteroids in the management of asthma.* Advances in therapy, 2023. **40**(6): p. 2577-2594.
4. Kumar, K., T.S. Hinks, and A. Singanayagam, *Treatment of COVID-19-exacerbated asthma: should systemic corticosteroids be used?* American Journal of Physiology-Lung Cellular and Molecular Physiology, 2020. **318**(6): p. L1244-L1247.
5. Martinez-Garcia, M.A., et al., *Role of inhaled corticosteroids in reducing exacerbations in bronchiectasis patients with blood eosinophilia pooled post-hoc analysis of 2 randomized clinical trials.* Respiratory Medicine, 2020. **172**.
6. Maspero, J.F., et al., *The use of systemic corticosteroids in asthma management in Latin American countries.* World Allergy Organization Journal, 2023. **16**(4): p. 100760.
7. Peerboom, S., et al., *Predictors of a good response to inhaled corticosteroids in obesity-associated asthma.* Biochemical pharmacology, 2020. **179**: p. 113994.
8. Quint, J.K., A. Ariel, and P.J. Barnes, *Rational use of inhaled corticosteroids for the treatment of COPD.* npj Primary Care Respiratory Medicine, 2023. **33**(1): p. 27.
9. Singh, D., et al., *New versus old: the impact of changing patterns of inhaled corticosteroid prescribing and dosing regimens in asthma management.* Advances in Therapy, 2022. **39**(5): p. 1895-1914.

10. Watanabe, K., et al., *Use of systemic corticosteroids for reasons other than asthma in subjects with asthma.* Respiration, 2022. **101**(2): p. 109-115.
11. Al Sulaiman, K., et al., *The role of inhaled corticosteroids (ICS) in critically Ill patients with COVID-19: A multicenter, cohort study.* Journal of Intensive Care Medicine, 2022. **37**(2): p. 248-257.
12. Bafadhel, M., et al., *Inhaled corticosteroids for the treatment of COVID-19.* European Respiratory Review, 2022. **31**(166).
13. Halpin, D.M., D. Singh, and R.M. Hadfield, *Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective.* European Respiratory Journal, 2020. **55**(5).
14. Jackson, D.J. and L.B. Bacharier, *Inhaled corticosteroids for the prevention of asthma exacerbations.* Annals of Allergy, Asthma & Immunology, 2021. **127**(5): p. 524-529.
15. Kearns, N., et al., *Inhaled corticosteroids in acute asthma: a systemic review and meta-analysis.* The Journal of Allergy and Clinical Immunology: In Practice, 2020. **8**(2): p. 605-617. e6.
16. Maijers, I., et al., *Oral steroid-sparing effect of high-dose inhaled corticosteroids in asthma.* European Respiratory Journal, 2020. **55**(1).
17. Marghli, S., et al., *Nebulized budesonide combined with systemic corticosteroid vs systemic corticosteroid alone in acute severe asthma managed in the emergency department: a randomized controlled trial.* BMC Emergency Medicine, 2022. **22**(1): p. 134.
18. Rodriguez-Martinez, C.E., M.P. Sossa-Briceño, and J.A. Castro-Rodriguez, *Advantage of inhaled corticosteroids as additional therapy to systemic corticosteroids for pediatric acute asthma exacerbations: a cost-effectiveness analysis.* Journal of Asthma, 2020. **57**(9): p. 949-958.
19. Shang, W., et al., *The safety of long-term use of inhaled corticosteroids in patients with asthma: a systematic review and meta-analysis.* Clinical Immunology, 2022. **236**: p. 108960.
20. Tan, D.J., et al., *Does the use of inhaled corticosteroids in asthma benefit lung function in the long-term? A systematic review and meta-analysis.* European Respiratory Review, 2021. **30**(159).