

## Research Paper

# Prescribing patterns and cost-utility analysis of management of childhood asthma in Saudi Arabia: a retrospective cross-sectional study

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Study place: This retrospective observational study was carried out in Al-Mana Group of Hospital (AGH), Al-Khobar, Saudi Arabia. AGH Al-Khobar is a 250-bedded teaching private hospital with 74 outpatient clinic to provide healthcare facilities to the community of Saudi Arabia.

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## Abstract

**Objective** This study is based on a retrospective cross-sectional study to assess the prescribing patterns and cost-utility analysis of management of childhood asthma in Saudi Arabia.

**Methods** Prescription data were collected for 1 year from electronic records of pharmacy. The unit dose price was retrieved from pharmacy database and compared with daily price based on WHO Defined Daily Dose (DDD) and Saudi Initiative for Asthma (SINA). The cost of each drug is calculated from average prices of each unit dose of each prescription.

**Key findings** In male children (57.98%), asthma was more common in comparison to female children (41.02%) at the studied hospital. Salbutamol (44.55%) was the most commonly prescribed medication followed by budesonide (30.97%) and montelukast (12.82%), whereas prednisolone (0.15%) was the least prescribed medication for the management of childhood asthma. It was found that fixed-dose combination of budesonide and formoterol prescribed for the longest duration of therapy (30 days) and imposed highest cost as well [197.10 SR (52.53 USD)] among all the prescribed medicine.

**Conclusion** In this study, inhalation route is the most preferred one for management of asthma; this may be due to their fast therapeutic action. Salbutamol was the most popular drug for quick reliever therapy, while budesonide was the most favoured drug for childhood asthma management. Medication prescribed for the management of childhood asthma at the mentioned study centre adhere to SINA guideline.

**Keywords:** asthma; prescribing patterns; cost-utility analysis; salbutamol; Saudi Initiative for Asthma; Saudi Arabia

## Introduction

Chronic respiratory diseases are a wide range of respiratory diseases related mainly to airways and other complications of lungs, asthma

being one of the prominent among these diseases. It results from airway hyper-responsiveness to various stimuli causing wheezing, coughing, night symptoms, activity limitation and difficulty in

breathing.<sup>[1]</sup> Two large multinational studies, the International and the European (ISAAC and ECRHS), have assessed the asthma prevalence across the globe and concluded that almost 300 million people suffer from asthma irrespective of their ages, ethnicity, environmental factors or backgrounds.<sup>[2,3]</sup> A study estimated that, by 2025, number of patients will increase to 100 million.<sup>[4]</sup> Even though its prevalence is among all age groups, it is the most occurring chronic illness of childhood. It accounts for missing school days, frequent visits to emergency room department, hospitalization, and may deprive the children of academic achievement and social interaction.<sup>[5]</sup> However, it has been predicted that the asthma prevalence may decrease with time and possibly may come to an end in some countries.<sup>[7,8]</sup> It is one of the commonest chronic diseases in Saudi Arabia, affecting over 2 million people.<sup>[9]</sup> Different results were reported by various studies conducted in Saudi Arabia about the commonness of childhood asthma, Abha region reported to have the lowest prevalence, whereas Alhofuf region had the highest prevalence.<sup>[10]</sup> Overall, its prevalence has risen from 8% to 23% between 1986 and 1995 in school children.<sup>[9]</sup> Also, local reports suggest that the asthma prevalence is increasing.<sup>[11,12]</sup>

Paediatric pulmonology suggests the Strategy of Asthma management in children, which includes steps such as establishing diagnosis, assessment of asthma control combined with proper pharmacotherapy, patient education, action plan and prevention.<sup>[6]</sup> As per SINA updated guidelines that are in concurrence with International and British asthma management guidelines, a stepwise approach to instituting and adjusting daily controller anti-inflammatory therapy is recommended beginning with monotherapy and then with combinations as per need. The primary therapy starts with salbutamol (Short-Acting Beta Agonists (SABA)) as needed; if it fails to achieve control, then a low to moderate or short courses of high-dose inhaled corticosteroid (ICS) are given, and then the treatment is recommended to be stepped-up until asthma is in control. Control is sustained for a period of 3 months, and then treatment can be stepped-down. Controller therapy includes modifying the dose of ICS with inhaled long-acting  $\beta_2$ -agonist (LABA) or leukotriene receptor antagonist (LTRA) for children aged 5 years or more, whereas in younger ones, the British guidelines recommend an LTRA for those who cannot or will not use ICSs.<sup>[13,14]</sup> Recent findings place more importance on using LTRA as a substitute to ICS at all ages.<sup>[15]</sup> But in general, it has been found that children with asthma are rarely treated with LTRA, a monotherapy with ICS is the most effective first-line controller monotherapy at all levels of severity.<sup>[16]</sup>

Asthma imposes a severe economic burden on healthcare systems. Annually, the direct cost of asthma was 88 million dirham in United Arab Emirates (UAE), 37.2 million USD in the USA, and 27 014 735 Omani Riyals in Oman.<sup>[17–19]</sup>

The objective of this retrospective cross-sectional study was to describe prescribing patterns and cost-utility analysis of management of childhood asthma in Saudi Arabia.

## Methods

This study was designed as a single-centred, cross-sectional retrospective pharmacy database study of prescribing patterns and cost-utility analysis of management of childhood asthma in Saudi Arabia. Data for the period from 1 January 2019 to 31 December 2019 were retrieved from the electronic pharmacy records in Al-Mana General Hospital Khobar, Saudi Arabia. Together, inpatient and outpatient pharmacy department electronic drug dispensing records were retrieved. All retrieved data were archived in Microsoft excel 2013.

Both sex children, any nationality asthmatic children patients aged up to 12 years and either new or old asthma-diagnosed children on therapy of asthmatic drug were included in the study. Patients who were not prescribed and dispensed any medications for management of childhood asthma were excluded from the study. Any asthma patients aged more than 12 years were also excluded from the study. The unit-dose prices of childhood asthma management drugs were also retrieved from pharmacy electronic drug dispensing record. Daily price of each drug was computed based on the World Health Organization (WHO) Defined Daily Dose (DDD) and Saudi Initiative for Asthma (SINA), which was established as a universal measure of drug consumption and provides a rough estimation of the prescribing pattern of different medications taken for childhood asthma management. The cost analysis of each studied drug was calculated in terms of average prices of each unit dose of each prescription. Last, the prescribing pattern was evaluated based on the adherence of guidelines and protocols of the SINA, which are the followed guidelines at the study centre (hospital) used for childhood asthma management. All the childhood asthma management drugs were categorized on the basis of availability of dose form and route of administration also coded in WHO anatomical therapeutic chemical classification code/ATC. These included the childhood asthma management drugs (nine drugs), for example, budesonide (ATC code: R03BA02), budesonide, formoterol (R03AK07), fluticasone furoate (ATC code: R01AD12), fluticasone propionate (ATC code: R01AD08), ipratropium bromide (ATC Code: R03BB01), montelukast (ATC code: R03DC03), salbutamol (ATC code: R03AC02), prednisolone (ATC code: R01AD02) and salmeterol, fluticasone propionate (R03AK06).

## Data analysis

Demographic characteristics were demonstrated as frequencies and percentages (with Wilson 95% confidence intervals for proportions). The chi-square test (for *P*-value calculation) was used to compare the adherence of SINA guideline used for prescribing the childhood asthma management therapy in Saudi Arabia. All statistical analyses were conducted using SPSS version 26 (SPSS Institute Inc., Cary, NC, USA) and Microsoft Excel 2013. *P*-value  $\leq 0.05$  was considered statistically significant.

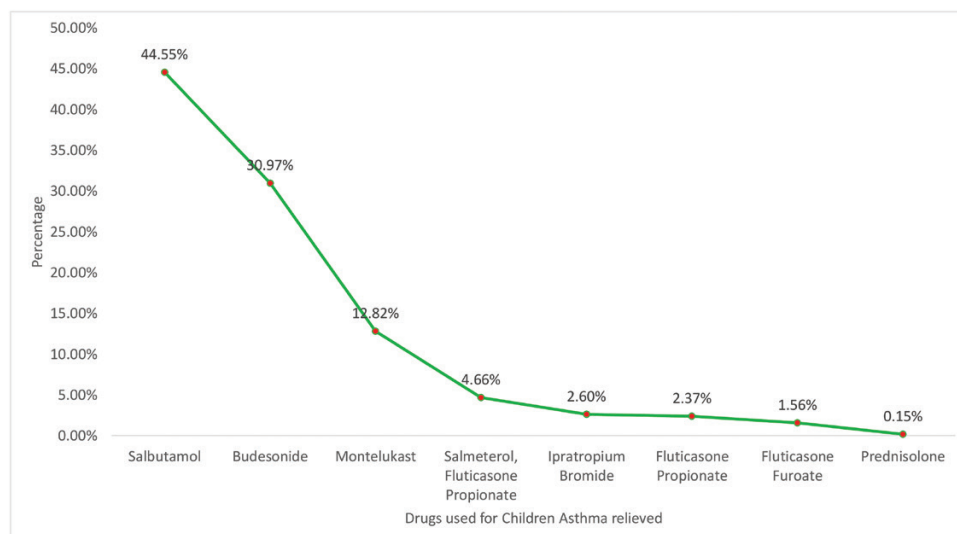
## Results

### Demographic characteristics

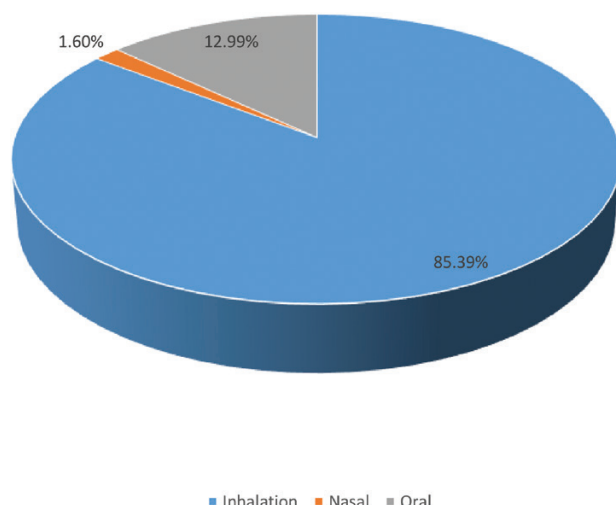
Table 1 shows the baseline demographic characteristics of 9404 studied patients. From the data collected, it was obvious that

**Table 1** Demographic characteristics of study participants (*n* = 9404).

Characteristics	Total 9404,% (95% CI) ( <i>n</i> )
Gender	
Male	57.98% (56.99–58.99) (5453)
Female	41.02% (41.02–43.01) (3951)
Age (years)	
<4	47.49% (46.48–48.5) (4466)
4–6	22.76% (21.93–23.63) (2141)
>6	29.74% (28.82–30.67) (2797)
Nationality	
Saudi	43.10% (42.11–44.11) (4054)
Non-Saudi	56.89% (55.89–57.89) (5350)



**Figure 1** Percentage wise prescribing patterns of childhood asthma management medication in study hospital.



**Figure 2** Route of administration of prescribed drug for management of childhood asthma in the studied hospital.

male children accounted for the majority of patients in the study [57.98% (5453)], compared with female children [41.02% (3951)]. The highest proportion of children were aged less than 4 years old (47.49%,  $n = 4466$ ), followed by children aged older than 6 years (29.74%,  $n = 2797$ ), and the lowest proportion were children aged between 4 and 6 years old (22.76%,  $n = 2141$ ). The number of non-Saudi patients [5350 (56.89%)] was more compared with Saudi patients [4054 (43.10%)].

### Prescribing patterns of management of childhood asthma therapy in the study hospital

Figure 1 shows that prescribing pattern of eight different types of drugs that were used for asthma management for the children in the studied hospital. It was clear that salbutamol was the most used drug, with a high percentage of 44.55%, followed by budesonide (30.97%), montelukast (12.82%), fixed dose of salmeterol with fluticasone propionate (4.66%), there was a marginal difference in the use of ipratropium bromide (2.60%) and fluticasone propionate

(2.37%). Least controller therapies used were fluticasone furoate (1.56%) and prednisolone (0.15%).

Prescribing patterns of management of childhood asthma in the studied hospital reflect the adherence of Saudi Initiative for Asthma (SINA) guidelines.<sup>[20]</sup>

### Route of administration

Figure 2 describes the route of administration used for management of childhood asthma relive therapy in the studied hospital. According to the data, it shows that the inhalation route was significantly larger route of administration 85.39%, compared to oral 12.99%, and the least commonly used was nasal route 1.60%.

Route of administration used for management of childhood asthma in the studied hospital adheres with Saudi Initiative for Asthma (SINA) guidelines.<sup>[20]</sup>

Table 2 outlines prescribing patterns for management of childhood asthma and adherence on SINA with percentage, Wilson 95% CI and frequency ( $n$ ).

Overall, salbutamol (R03AC02) 2.5 mg given by inhalation was the most prescribed medication [44.55% (43.56–45.57) 4190,  $P$ -value  $\leq 0.05$ ], with higher percentage among children aged less than 4 years old [22.04% (21.21–22.89) 2073], compared with 4–6 years old [13% (12.35–13.72) 1224] and >6 years old [9.50% (8.92–10.11) 893], followed by budesonide (R03BA02) sterile nebulizer suspension, 0.25–0.5 mg BD [30.97% (30.13–32.0) 2921,  $P$ -value  $\leq 0.05$ ], given by inhalation, with higher percentage among children aged less than 4 years old [17.30% (16.55–18.08) 1627], compared with 4–6 years [5.45% (5.02–5.94) 513] and >6 years [8.30% (7.76–8.87) 781], montelukast (R03DC03), oral powder, 4 mg [12.82% (12.16–13.51) 1206], for children <4 years old and >6 years old [4.66% (4.26–5.12) 439], while children 4–6 years old [3.48% (3.14–3.88) 328], salmeterol, fluticasone combination (R03AK06), pressurized inhalation, suspension, 25 µg salmeterol and 50 µg fluticasone propionate twice daily [4.66% (4.26–5.12) 439,  $P$ -value  $\leq 0.05$ ], with higher percentage for age group > 6 years old [2.28% (2.01–2.61) 215], compared with 4–6 years old [2.03% (1.76–2.34) 191] and <4 years old [0.35% (0.25–0.49) 33], ipratropium bromide (R03BB01), nebulizer solution, 125–250 µg given by inhalation

**Table 2** Prescribing patterns for management of childhood asthma and adherence on Saudi Initiative for Asthma (SINA) ( $n = 9404$ )

Drug	ATC code	Dosages form	Route of administration	Dose	Total 9404,% (95% CI) ( $n$ )	<4 years % (95% CI) ( $n$ )	4–6 years % (95% CI) ( $n$ )	>6 years % (95% CI) ( $n$ )	$P$ -value
Budesonide	R03BA02	Sterile nebulizer suspension	Inhalation	0.25–0.5 mg BD	30.97% (30.13–32.0) (2921)	17.30% (16.55–18.08) (1627)	5.45% (5.02–5.94) (513)	8.30% (7.76–8.87) (781)	$\leq 0.05$
Budesonide, Formeterol	R03AK07	Inhalation powder	Inhalation	100 µg/6 µg/inhalation	4	0	0	4	-
Fluticasone Furoate	R01AD12	Nasal spray, suspension.	Intranasal, Inhalation	55 µg	1.56% (1.33–1.83) (147)	0.22% (0.14–0.34) (21)	0.62% (0.49–0.81) (59)	0.71% (0.56–0.9) (67)	$\leq 0.05$
Fluticasone Propionate	R01AD08	Pressurized inhalation, suspension	Intranasal, Inhalation	50–100 microgram BD	2.37% (2.08–2.70) (223)	1.1% (0.91–1.33) (103)	0.59% (0.46–0.78) (56)	0.82% (0.67–1.03) (78)	0.0091
Ipratropium Bromide	R03BB01	Nebulizer solution	Inhalation	125–250 µg	2.60% (2.31–2.95) (245)	1.78% (1.54–2.08) (168)	0.48% (0.37–0.65) (46)	0.32% (0.23–0.47) (31)	$\leq 0.05$
Montelukast	R03DC03	Oral powder/ Granules, Tablet	Oral	4 mg	12.82% (12.16–13.51) (1206)	4.66% (4.26–5.12) (439)	3.48% (3.14–3.88) (328)	4.66% (4.26–5.12) (439)	$\leq 0.05$
Salbutamol	R03AC02	Solution for nebulization	Inhalation	2.5 mg	44.55% (43.56–45.57) (4190)	22.04% (21.21–22.89) (2073)	13% (12.35–13.72) (1224)	9.50% (8.92–10.11) (893)	$\leq 0.05$
Prednisolone	R01AD02	Tablet	Oral	5 mg	0.15% (0.1–0.26) (15)	-	-	0.15% (0.1–0.26) (15)	-
Salmeterol, Fluticasone Propionate	R03AK06	Pressurized inhalation, suspension.	Inhalation	25 µg Salmeterol and 50 µg fluticasone propionate twice daily	4.66% (4.26–5.12) (439)	0.35% (0.25–0.49) (33)	2.03% (1.76–2.34) (191)	2.28% (2.01–2.61) (215)	$\leq 0.05$

[2.60% (2.31–2.95) 245,  $P$ -value  $\leq 0.05$ ], higher in age group < 4 years old [1.78% (1.54–2.08) 168], compared with 4–6 years [0.48% (0.37–0.65) 46] and >6 years [0.32% (0.23–0.47) 31], fluticasone propionate (R01AD08), in the form of pressurized inhalation, suspension, 50–100 µg BD, given by inhalation/intranasal route [2.37% (2.08–2.70) 223,  $P$ -value = 0.0091], higher in age group <4 years [1.1% (0.91–1.33) 103], compared with 4–6 years [0.59% (0.46–0.78) 56] and >6 years [0.82% (0.67–0.93) 78], fluticasone furoate (R01AD12), 55 µg, in form of nasal spray/suspension, given by intranasal and inhalation route, [1.56% (1.33–1.83) 147,  $P$ -value  $\leq 0.05$ ], higher in age group > 6 years [0.71% (0.56–0.9) 67], compared with 4–6 years [0.62% (0.49–0.81) 59] and <4 years [0.22% (0.14–0.34) 21], the least drugs prescribed were found to be prednisolone (R01AD02), tablet, 5 mg given orally [0.15% (0.1–0.26) 15] to children age older than 9 years, and budesonide, formeterol (R03AK07), inhalation powder, 100 µg/6 µg/inhalation, given by inhalation ( $n = 4$ ) to children age older than 6 years.

Most of the prescribed drugs have shown  $P$ -value  $\leq 0.05$ , which means that prescribers adhere to SINA guidelines.

Table 3 shows the management of childhood asthma drugs approved by SFDA for marketing in Saudi Arabia with average therapy of duration in days and average cost unit-dose prescription wise in SR (USD).

There were nine drugs approved by SFDA for marketing in Saudi Arabia for management of childhood Asthma (Table 3). The duration of patient therapy ranged from 38.95 days for montelukast (R03DC03), 30 days for budesonide, formeterol (R03AK07), 28.22 days for fluticasone propionate (R01AD08), 19.57 days for fluticasone furoate (R01AD12), 12.20 days for prednisolone (R01AD02), 7.71 days for budesonide (R03BA02), 5.66 days

for ipratropium bromide (R03BB01), 6.80 days for salbutamol (R03AC02) and 6.80 days for salmeterol, fluticasone propionate (R03AK06). Cost-wise unit-dose prescription was found to be highest for budesonide, formeterol combination [197.10 SR (52.53USD)], followed by fluticasone propionate [76.26 SR (20.32USD)], fluticasone furoate [52.1 SR (13.89USD)], prednisolone [22.53 SR (6.00USD)]; same cost was shown for salbutamol and salmeterol, fluticasone propionate [15.56 SR (4.15USD)], budesonide [7.78 SR (2.07USD)], montelukast [4.60 SR (1.23USD)], making ipratropium bromide as the cheapest drug [1.68 SR (0.45USD)].

## Discussion

In the contemporary study, data for paediatric population were collected from a hospital for the duration of 1 year and analysed for determining the trend in using asthma management medications and analysing their costs. Childhood asthma management medications were used to attain and retain control of persistent asthma. They are used alone or in combination depending on the stage of the persistent asthma and are administered by either nasal inhalation or oral inhalation.<sup>[20]</sup> In the present study, there is a high prevalence of the use of the inhalation route administered asthmatic drugs compared with the other routes. In fact, inhalation route is the most preferred drug delivery system because it allows the drugs to be transported directly to the airways with faster onset of action and fewer side effects.<sup>[21,22]</sup>

The male children (57.98%) of population accounted for the majority of asthmatic patients in the current study. In comparison between genders, many studies have reported that male children are constantly at higher risk of asthma, which has been explained by variance growth of lung/airway size and immunological

**Table 3** Childhood asthma management medicine approved by SFDA for marketing in Saudi Arabia and their cost-utility analysis prescription wise

Drug (ATC code)	Dose	Average therapy of duration in days	Average cost in unit-dose prescription wise in SR (USD)
Budesonide (R03BA02)	0.25–0.5 mg BD	7.71	7.78 (2.07)
Budesonide , Formeterol (R03AK07)	100 µg/6 µg/inhalation	30	197.10 (52.53)
Fluticasone Furoate (R01AD12)	55 µg	19.57	52.1 (13.89)
Fluticasone Propionate (R01AD08)	50 to 100 microgram BD	28.22	76.26 (20.32)
Ipratropium Bromide (R03BB01)	125–250 µg	5.66	1.68 (0.45)
Montelukast (R03DC03)	4 mg	38.95	4.60 (1.23)
Salbutamol (R03AC02)	2.5 mg	6.80	15.56 (4.15)
Prednisolone (R01AD02)	5 mg	12.20	22.53 (6.00)
Salmeterol, Fluticasone Propionate (R03AK06)	25 µg Salmeterol and 50 µg fluticasone propionate twice daily	6.80	15.56 (4.15)

modifications.<sup>[23,24]</sup> Moreover, the high prevalence of asthma among children aged less than 4 years (47.49%) revealed in this study matches with the results of another recent study conducted in Saudi Arabia in 2019.<sup>[25]</sup> Additionally, non-Saudi patients (56.89%) were predominant in contrast to Saudi patients (43.10%). However, this observation unmatched with another study done to evaluate the prevalence of asthma among Saudi and non-Saudi children, where the majority of asthmatic patients were Saudi.<sup>[26]</sup>

In line with the SINA guidelines, the prevalent childhood asthma controlled by monotherapy in the present research was ICS, that is, budesonide recommended for about 30.97% of the studied asthmatic cases followed by montelukast (12.82%). Many studies have proved that both budesonide and montelukast are efficacious and well tolerated in paediatric asthma. However, more preference is given to budesonide. Also, the cost price of montelukast is higher than budesonide.<sup>[27,28]</sup> Moreover, ICS is the preferred option for most paediatric age range.<sup>[20]</sup> Likewise, research conducted in Saudi Arabia in 2017 to evaluate the drug utilization in asthmatic patients reveals that salbutamol followed by budesonide was the most commonly prescribed drugs.<sup>[26]</sup>

On the other hand, the low percentage of the prescriptions for the combination therapy of LABA/ICS could be explained by the scarcity of recommendations to be used in children less than 4 years, and this combination is usually used as maintenance therapy in mild-moderate persistent asthma. On contrast to SINA recommendations, salmeterol/fluticasone propionate combination therapy was used more often than formeterol/budesonide, which could be due to the pharmaceutical cost of the latter is higher than the former. Based on the SINA guidelines and many other studies, it is cost-effective to use salmeterol/fluticasone propionate combination therapy compared with doubling fluticasone propionate dose.<sup>[29]</sup> This pattern is confirmed by the results of the current study.

In congruence with SINA guidelines and many studies that recommend the SABA 'as needed' to relieve symptoms while the patients undergoing controller therapy, we found nearly 45% of the studied patients had prescriptions for Salbutamol.<sup>[16,20]</sup> In addition, it has been observed that the usage pattern of short-acting anticholinergic is low around 2.6% as it is less potent in asthma and more beneficial once added to SABA.<sup>[20,30]</sup>

## Conclusion

Our study declared that the inhalation route was the desired method of administration of asthmatic drugs for children. Salbutamol was the most popular reliever therapy, while budesonide was the most

favoured asthma controller monotherapy used among children in all age group. Our study revealed that asthmatic drug utilization pattern in paediatric is mostly compliant with SINA guidelines, which reflect physician's awareness and concurrence of updated guidelines. Moreover, the implementation of these guidelines will reduce economic medical burden of the disease and will maximize the benefit of the therapy, contributing to better quality of life to the asthmatic patients. Although medication prescribing at the mention study centre is adhere to guideline, but their safe and effective use of medication should be warranted, also there must be proper way of adverse drug reaction reporting should follow if appeared by the use of medication.

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## Author Contributions

M.D.A. designed the study, analysed data, and drafted the study. A.Y. and M.P. also analysed data and proofread the study. N.B., S.A.G. and Z.E. reviewed and edited the drafted study. All Authors state that they had complete access to the study data that support the publication.

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## Conflict of Interest

None declared.

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