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Comparing Global Initiative for Asthma guideline approaches to asthma control in adolescents aged 12 and above

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Abstract

The Global Initiative for Asthma (GINA) guidelines for asthma management in children and adolescents aged 12 years and older present two treatment tracks. Track 1, the preferred option, involves as-needed low-dose inhaled corticosteroids (ICS) combined with formoterol. Track 2 involves as-needed ICS with a short-acting β-agonist for step 1 and low-dose maintenance ICS for step 2. This study aimed to compare the effectiveness of Track 1 and Track 2 in managing asthma in pediatric patients aged 12 years or older. This was a retrospective study that was conducted at Aga Khan University Hospital in Karachi, Pakistan, from January 1, 2022, to December 31, 2023. The study included children and adolescents aged 12 years or older, diagnosed with asthma exacerbations, who were discharged on reliever therapy following the GINA guidelines for steps 1 and 2. Patients were followed for re-admission within 30 days, emergency room (ER) visits, annual admissions, length of stay, and the need for intensive care. Pulmonary function tests (PFTs) were performed at 1 week and 3 months post-discharge. A total of 90 patients were enrolled and divided into Track 1 (n=43) and Track 2 (n=47). Track 1 patients had significantly fewer readmissions (4.65% *vs.* 19.15%, p=0.036), fewer ER visits (1.69±1.31 *vs.* 2.8±1.37, p<0.001), and fewer hospital admissions (1.37±0.85 *vs.* 2.1±0.84, p<0.001). Track 1 patients also required less intensive care (9.3% *vs.* 27.66%, p=0.034). PFTs showed greater improvement in forced expiratory volume in one second **(**FEV1) and the FEV1/forced vital capacity ratio for Track 1 compared to Track 2 at three months (p=0.026 and p<0.001, respectively). The study found that treatment with as-needed ICS/formoterol (Track 1) was more effective in managing asthma compared to the alternative treatment strategies in Track 2.

Key words: asthma control, GINA guidelines, inhaled corticosteroids, formoterol, short-acting β-agonists.

Introduction

Asthma is a serious global health problem, and it impacts 4.3% of the population of Pakistan- the world's fifth most populated country [1,2]. It is defined as a heterogenous disease usually characterized by chronic airway inflammation [2,3]. Asthma presents with a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary with time and in intensity [3]. The Global Initiative for Asthma (GINA) aims to improve the diagnosis, management, and prevention of asthma [2]. It provides guidelines that are based on a stepwise approach with treatment progressively increased to achieve asthma symptom control and reduce the risk of exacerbation, with the option to reduce treatment doses after a period of symptom control [4].

The 2023 GINA guidelines for children and adolescents aged 12 years and older offer two tracks that can be followed for the management of mild asthma. Track 1, which is the preferred track advises the usage of as needed low dose inhaled corticosteroids (ICS) and formoterol combination [3]. The alternative track, track 2, advises using ICS whenever a short-acting beta-agonist (SABA) is used for step 1 and using a low dose maintenance ICS for step 2 [3]. Track 1 is the preferred overall approach due to several reasons, namely due the fact that it reduces the risk of severe exacerbations as compared to using a SABA reliever, while also achieving similar symptom control, similar lung function, and a lower oral corticosteroid burden [2]. As needed ICS/formoterol is preferred for steps 1 and 2 because patients with mild asthma can have severe exacerbations, adherence to daily ICS is largely poor, and patients taking SABA alone tend to regard it as their main asthma treatment [2].

This recent shift of the GINA guidelines from SABA is due to the substantive risks that accompany it [5]. These risks arise due to the long-term effects of using SABA as well as the overuse of SABA in severe attacks [5]. Moreover, inhaled corticosteroids alleviate chronic inflammation in contrast to SABA [6]. Formoterol is a long-acting beta agonist (LABA) that has rapid pharmacokinetic effects comparable to that of SABAs [6].

Freedom of choice given by GINA guidelines allows for variable practices among physicians. The objective of our study was to compare the effectiveness of Track 1 and 2 for control of asthma in steps 1 and 2 in pediatric patients aged 12 years or older. Our aim was to assess how Track 1 may be more beneficial than Track 2 for asthma control in patients aged 12 years of older in our population.

Materials and Methods

A retrospective study starting from January 1, 2022 to December 31, 2023 was conducted at Aga Khan University Hospital in Karachi, Pakistan. Ethical approval was taken from institution

ethics review committee (ID-10083) before commencement of the study. Children and adolescents aged 12 years or older who were diagnosed and admitted with asthma exacerbations and were then discharged on reliever therapy using the GINA guidelines for step 1 and 2 for asthma control for 3 months were the subjects of interest in this study. As previously mentioned, the GINA guidelines have two tracks that can be followed for control of asthma, and this allows physicians and patients the freedom to choose their preferred treatment options. The GINA guidelines allow physicians to have autonomy when deciding on a treatment plan based on their own decisions and patient's preferences. According to this, the study participants were divided into two groups: those who followed track 1 and those on track 2. Track 1 requires that patient that the patient use as needed ICS/formoterol for steps 1 and 2. Whereas, track 2 demands as needed ICS/SABA for step 1 and a maintenance low-dose ICS with as- needed SABA for step 2. This can be visualized in Table 1.

In track 1, the low dose ICS /formoterol was 200ug/6ug per day (ICS= Budesonide or beclomethasone equivalent) as per GINA guideline whereas at track 2 -step 1, the dose of ICS/SABA is 100-200ug each per day. Salbutamol was used as SABA where ICS was Beclomethasone. In track 2, -step 2, low dose ICS was 200ug to 400ug of Beclomethasone equivalent.

The patients following discharge were followed for re-admission within 30 days of discharge, number of ER visits with asthma exacerbations per year, mean admission with asthma per year, average length of stay per admission, and the need for special or intensive care. Pulmonary function tests were also obtained 1 week post discharge and 3 months post discharge (Figure 1). This was done using electronic medical records that documents every patient's hospital visit. Patients were on the same treatment plan as at the time of discharge.

Pediatric patients who were lost to follow-up, with no pulmonary function tests performed 1 week or 3 months after discharge, or with an incomplete medication history were excluded from the study. Patients who were managed on any other step besides step 1 and 2 as per the GINA guidelines for control of asthma following discharge were excluded from the study. Moreover, patients previously admitted with upper airway obstruction, bronchopneumonia, bronchiolitis, previously diagnosed chronic lung disease, cystic fibrosis, congenital cardiac disease, tuberculosis, and immune deficiency syndrome were also excluded from the study.

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) define an asthma exacerbation as a worsening of symptoms, lung function, and/or an increased use of rescue bronchodilators lasting at least two days [7].

Pulmonary function tests were conducted using the Easy-On-PC® device, and the interpretation of FEV1 readings, the FEV1/FVC ratio, and other parameters followed the guidelines set by the American Thoracic Society and the European Respiratory Society [7].

Results

This study consisted of a total of 90 pediatric patients aged 12 years or older who were enrolled and then divided into 2 categories- track 1 and track 2. Track 1 consisted of 43 (47.78%) and track 2 consisted of 47 (52.22%) patients. In track 1, out of 43 patients, 21 (48.83%) patients were on step 1and 22 (51.16%) patients were on step 2. In Track 2, there were 25 (53.19%) patients were labelled as on step 1 and 23 (48.93%) were on step 2.

There was no significant difference between the demographic variables such as age, gender, and BMI between the two groups. There was a significant difference in re-admission within 30 days of discharge with patients following Track 1 and those following Track 2 (4.65% vs. 19.15%, p=0.036). There was also a similar significant relationship in ER visits with asthma exacerbations in patients in Track 1 group having 1.69±1.31 and those in the Track 2 group having 2.8±1.37 ($p<0.001$). Furthermore, the Track 1 group had a lower mean admission with asthma per year (1.37±0.85) than the Track 2 group (2.1±0.84) ($p<0.001$). There were also significantly fewer patients in Track 1 requiring intensive care, 4 (9.30%), as compared to those in Track 2, 13 (27.66%) with p=0.034. There was no significantly different relationship between the Track 1 and Track 2 groups in average length of stay per admission and number of patients needing special care (Table 2).

FEV1 and FEV1/FVC ratio was obtained for 1 week and 3 months post-discharge among the two groups using a hand-held spirometer to record lung function parameters. Both groups show no significant differences in the FEV1 and FEV1/FVC ratio within one week after discharge. However, there was a significant improvement in FEV1 three months after discharge with a greater improvement in Track 1 (89.23±9.12) than in Track 2 (84.57±10.32) (p=0.026) (Table 3). There is also a significant improvement in the FEV1/FVC ratio three months post-discharge with a greater improvement in Track 1 (89.79±10.15) as compared to Track 2 (82.38±9.81) with $p<0.001$. This can also be
visualized in Figure 2.

Discussion

This study focuses on children and adolescents aged 12 years or older who were admitted with asthma exacerbation and subsequently discharged following either track 1 or 2 of steps 1 and 2 of the GINA guidelines. Through this study, we were able to ascertain how Track 1 is more

beneficial than Track 2 in our population. This was seen by the significant difference in re-admission within 30 days of discharge with Track 1 group having fewer re-admissions in comparison to Track 2 group. Moreover, Track 1 group also presented with significantly less ER visits with asthma exacerbation per year than the Track 2 group. There was also a decrease in mean admission with asthma per year as well as number of patients requiring intensive care in patients following Track 1 than those following Track 2.

Furthermore, while both groups showed an improvement in lung function parameters, Track 1 showed a significantly greater improvement in lung function tests 3 months after discharge as compared to Track 2. There was an improvement in both FEV1 and FEV1/FVC ratio values 3 months post discharge. Although, there was no significant difference in the average length of stay per admission and patients requiring special care between the groups.

A study conducted from several populations and hospital-based studies in sub-Saharan Africa highlighted that the prevalence of uncontrolled asthma ranged from 45% to 95% in adults and children. Low-middle-income countries (LMICs) have poor health-care resources and lack universal health coverage making the burden and impact of uncontrolled asthma higher as compared to developed countries. This emphasizes the need for low-middle-income countries to work towards the goal of achieving good asthma control [8].

The treatment of mild asthma as early as the 1930s used to be primarily SABAs [9]. However, in recent years it has been noticed that the overuse of SABA is associated with an increased risk of exacerbations and asthma-related mortality risk [9,10]. Studies have shown that regular use of SABA is associated with increased exercise bronchoconstriction and allergic airway inflammation [9]. Inhaled corticosteroids, on the other hand, are effective in reducing eosinophilic airway inflammation, asthma control and reducing asthma exacerbation risks [9]. Therefore, treatment options combined with inhaled corticosteroids are often referred to as 'anti-inflammatory reliever'(AIR). This brought up the idea of treatment of mild asthma with ICS combined with either SABA or formoterol, a fact-acting long-acting beta-agonist (LABA) [11].

In the TREXA study, it was presented that treatment with maintenance low-dose ICS reduced asthma exacerbation risk by 50% compared to SABA as a reliever alone. Moreover, ICS/SABA as a rescue medication was also seen to be more effective as reducing exacerbations than utilizing SABA reliever alone [12]. Another study by *Sumino et al.* showed that treatment with ICS/SABA reliever therapy was as effective as maintenance ICS for controlling asthma [13]. A randomized controlled trial conducted by *Rabe et al.* studies the effect of three groups – SABA, formoterol, and ICS/formoterol- as a reliever therapy for asthma exacerbations in patients receiving ICS/formoterol maintenance therapy [14]. This study showed that patients utilizing

budesonide-formoterol as-needed had fewer severe exacerbations (19 per year per 100 patients) as compared to the other two groups [14]. The utilization of ICS/formoterol as a reliever has been shown to reduce fractional exhaled nitric oxide, an indirect marker of airway inflammation, therefore exhibiting this combination as an AIR therapy [15].

The SYGMA 1 study consisted of pediatric patients with mild asthma who were divided into 3 groups- SABA reliever group, ICS/formoterol reliever group, and maintenance ICS with SABA reliever group. The studies showed that while reliever ICS/formoterol had a 64% lower rate of severe exacerbation compared to reliever SABA, there was no significant difference between the reliever ICS/formoterol group and the maintenance ICS group. Our study showed a similar result with significantly lesser visits with asthma exacerbation per year in the ICS/formoterol group as compared to the ICS/SABA group. It was also noted that though the ICS/formoterol group was inferior to the ICS maintenance group in achieving well-controlled asthma, the patients in the reliever ICS group were exposed to less than one fifth of the amount of inhaled corticosteroid [16]. The SYGMA 2 study was a similar study but without electronic diaries or adherence reminders with less involvement of the clinical research team to mimic a more real-world setting. In this study it was seen that the as needed ICS/formoterol was not significantly different from the low-dose maintenance ICS in terms of yearly rate of severe asthma exacerbations and the time to the first severe exacerbation with less than a quarter of the total exposure to inhaled glucocorticoid as received in the ICS maintenance group [17]. In the Novel START study, patients were randomly divided into 3 groups- as-needed SABA, maintenance ICS with as-needed SABA, and as-needed ICS/formoterol. This study showed that though as-needed ICS/formoterol had a lower asthma exacerbation rate as compared to as-needed SABA, there was no significant difference in comparison to the ICS maintenance group. This was also seen in terms of risk of exacerbation [18]. Another study conducted by *Lazarinis et al.* showed that as-needed ICS/formoterol was superior at reducing exercise induced bronchoconstriction as comparison to as-needed SABA [19]. Moreover, there was no difference between the as-needed ICS/formoterol and maintenance ICS for reduction in exercise induced bronchoconstriction [19].

The PRACTICAL study involved 885 patients who were randomly assigned to two groups- the ICS/formoterol reliever group and the maintenance ICS group with as-needed SABA. The ICS/formoterol reliever group was seen to have fewer severe exacerbations per patient per year in comparison to maintenance ICS and as-needed ICS [20]. Through this study, it was also noted that 65% of the 306 participants preferred the combined preventer and reliever therapy taken as needed and that 35% of the 306 participants preferred a twice-daily preventer inhaler with a reliever therapy as-needed [21]. We also noted in our study the patients requiring

intensive care was significantly less in the ICS/formoterol group as compared to ICS/SABA group.

A systematic review and meta-analysis conducted by *Hatter et al.* concluded that as-needed ICS/formoterol prolonged the time to first severe exacerbation in adults and adolescents with mild asthma as compared to maintenance ICS with as-needed SABA [22]. This makes the more widely available as-needed ICS/formoterol the more preferred treatment as in comparison to maintenance ICS with as-needed SABA for the treatment of mild asthma [23]. In our study, we found that the re-admission with asthma within 30 days of discharge was also significantly less in the ICS/formoterol group as compared to the ICS/SABA group.

Limitations

The limitations of our study include its retrospective design, which makes it challenging to assess compliance within the pediatric population as well as make a definite conclusion. This is a single-centre study making it difficult for us to assess the asthma control prevalence. Additionally, factors such as the climate during subsequent ER visits and exposure to triggering conditions were not considered, which could influence the need for specialized or intensive care. Future clinical trials will be essential in providing more robust evidence to address these questions.

Conclusions

It is imperative that we give the appropriate medication treatment to pediatric asthmatics to ensure optimal asthma control. Our study aimed at presenting the effectiveness of Track 1 over Track 2 in children and adolescents over the age of 12. Through this study, we aimed to encourage the use of an ICS/formoterol reliever combination over the more commonly utilized SABA. Our study concluded that treatment with ICS/formoterol was superior to that of either ICS/SABA or maintenance ICS with as-needed SABA.

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Table 1. Highlighting steps 1and 2 from the Global Initiative for Asthma guideline 2023.

	Step 1	**Step 2**
Track 1	As-needed ICS/formoterol	As-needed ICS/formoterol
Track 2	As-needed ICS/SABA	Maintenance low-dose ICS with as-needed SABA

ICS, inhaled corticosteroids; SABA, short acting β-agonist.

Table 2. Demographics and clinical variables.

	Track 1 group	**Track 2 group**	**p**	**t-value**	**Chi-square**
Patient n (%)	43 (47.78)	47 (52.22)			
Age (Years)	14.20±2.40	15.8±2.80	0.171	0.89	
Male: Female	1.4:1	1.5:1			
Body Mass Index (BMI)	16.67±2.36	17.23±1.94	0.145	0.84	
Average duration on diagnosis with asthma (years)	10.84±1.67	9.93±1.40	0.187	0.76	
Re-admission within 30 days of discharge (%)	2 (4.65)	9 (19.15)	0.036		4.399
ER visit with asthma exacerbation per year	1.69±1.31	2.8±1.37	<0.001	-3.90	
Mean admission with asthma per year	1.37±0.85	2.1±0.84	<0.001	-4.12	
Average LOS per admission	2.36±0.83	2.44±0.82	0.518	0.649	
Number of patients needing HDU care, n (%)	10 (23.26)	13 (27.66)	0.132		0.172
Number of patients needing PICU care, n (%)	4 (9.30)	13 (27.66)	0.034		4.939

Table 3. Lung function tests.

	Track 1 group	**Track 2 Group**	**p-value**
FEV1, Within one week after discharge (%)	75.32± 3.65	75.021±4,55	0.729
FEV1, Three months follow-up (%)	89.23±9.12	84.57±10.32	0.026
FEV1/FVC, within one week after discharge (%)	77.36±6.6	78.10±7.72	0.63
FEV1/FVC, three months follow-up (%)	89.79±10.15	82.38±9.81	<0.001

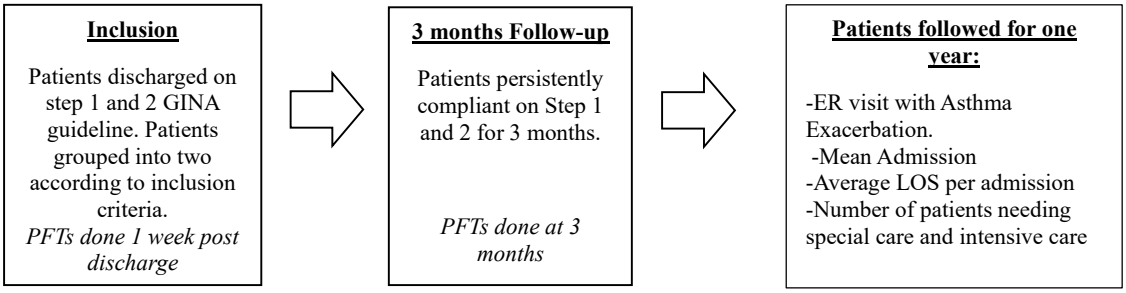

Figure 1. Study design.

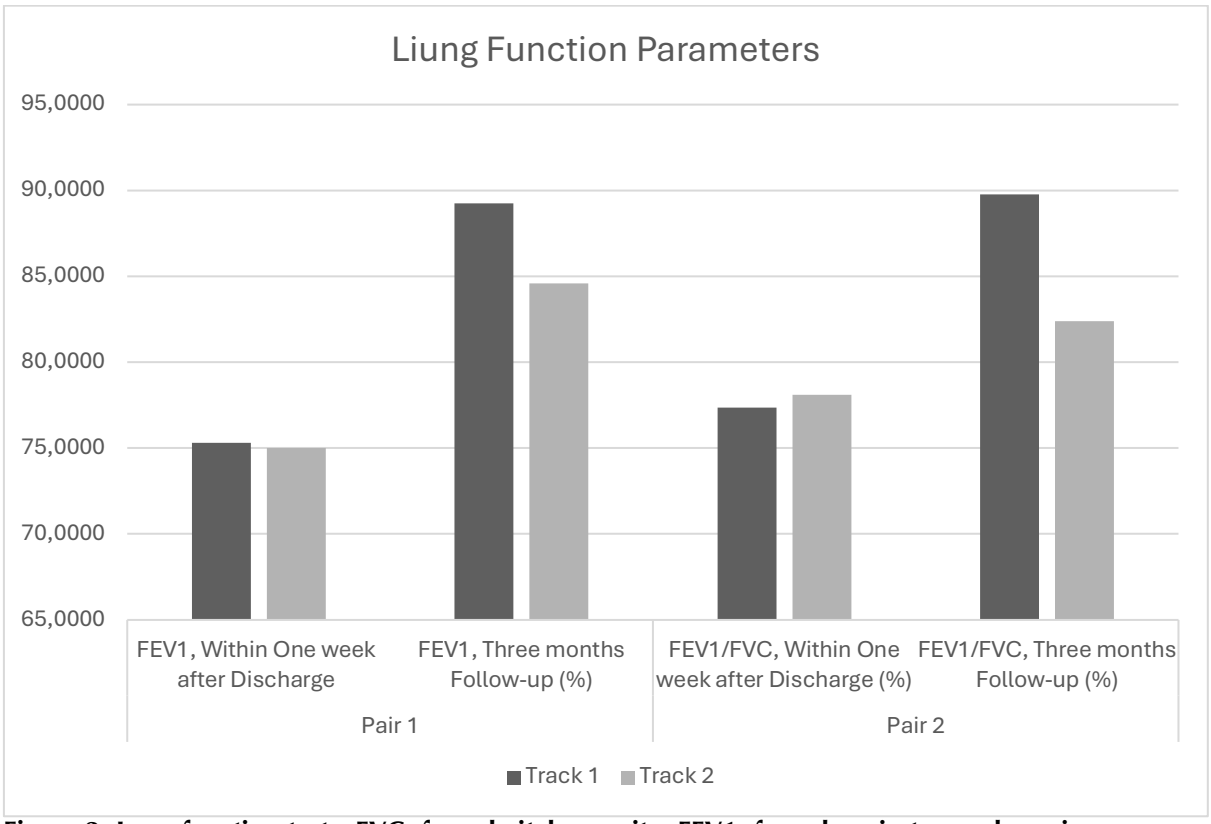

Figure 2. Lung function tests. FVC, forced vital capacity; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LABA: long acting β-agonist