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Factors Associated with Failure of Stepping-Down Treatment in Pediatric Asthma

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Abstract

Background The international and Thai asthma guidelines recommend stepping-down controller treatment in patients whose asthma symptoms have been controlled and maintained for 3 months or longer. After stepping-down treatment, some patients experienced exacerbations and required emergency care. There is limited understanding of stepping-down treatment for asthmatic children. The goal of this study was to determine the failure rate and associated factors after stepping-down treatment in pediatric asthma.

Methods A retrospective study of electronic medical records of asthmatic patients aged between 3 and 15 years with controlled symptoms and indications for stepping-down treatment was conducted at Maharat Nakhon Ratchasima Hospital, a tertiary care center in Northeast Thailand, between January 2015 and December 2019.

Results Of the 110 asthmatic patients with well-controlled asthma who received stepping-down treatment, 90 patients were followed over 12 months. Failure of treatment within 12 months of follow-up was 37.8% (34 of 90). Patients who failed to stepping-down treatment had asthma onset at a younger age ($p = 0.026$) and less than 9 months duration of asthma stability before stepping-down ($p = 0.049$). In multivariate analysis, the factor associated with failed stepping-down treatment was the length of asthma stability of fewer than 9 months with an odds ratio of 4.8 (95% confidence interval: 1.02–22.47).

Conclusion Stepping-down treatment in well-controlled pediatric asthma resulted in a high failure rate. The author suggests initiating stepping-down treatment in patients whose duration of asthma stability is greater than 9 months may improve the rate of success.

Keywords

- pediatric asthma
- stepping-down treatment
- failure of treatment
- well-controlled asthma
- asthma exacerbation

Introduction

Asthma is a chronic disease of airway inflammation, airway hyperresponsiveness, and variable expiratory airflow limitation due to inflammation. Patients usually have chest tightness, wheezing, shortness of breath, and cough.[1] In Thailand, asthma is an increasingly common disease, the prevalence of asthma in Thai children aged between 6 and 7 years was 7.8 to 15% in 2007.[2]

The international and Thai guidelines for asthma recommend using the least amount of medication necessary to optimally manage asthma symptoms. Stepping-down treatment should be considered if asthma is stable for 3 months or longer to decrease potential adverse drug reactions and minimize treatment costs.[1,3] Inhaled corticosteroid (ICS) is the mainstay treatment in asthmatic children. Suppression of growth[4] and the adrenal axis[5] have been reported as adverse effects of ICS treatment. There are many studies

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for stepping-up treatments, but there still are knowledge gaps concerning stepping-down treatments, especially in pediatric asthma. Many children with asthma have a remission of symptoms during adolescence providing a rationale that controllers could be reduced or stopped.[6,7] Some experts suggest stepping-down medications in children are frequently successful in well-controlled mild asthma and long-term cessation of ICS can be achieved in children in certain situations.[8,9] Additionally, it was found that stepping-down asthma medications in controlled patients can reduce treatment costs while suppressing asthma symptoms.[3]

In studies of adults with asthma, a step down of ICS increased the risk of asthma exacerbation and the use of reliever medications.[9–12] Predictors of failure in stepping-down treatment were the presence of comorbidities such as rhinitis, rhinosinusitis, the grade of phlegm,[11] in addition to older age, and greater severity of asthma.[12] In asthmatic children, decreased medication during the fall season is known to worsen the risk of failure in stepping-down treatment,[13] in addition to shorter lengths of asthma stability related to more frequent exacerbations.[14] There are few studies examining factors associated with failure of treatment after decreased asthma medications in children. The objective of this study was to examine the rate of failure and explore the factors associated with failure in stepping-down asthma treatment in pediatric patients.

Methods

This study was a retrospective review of electronic medical records of asthmatic patients aged between 3 and 15 years old at the Allergy and Chest Clinic, Maharat Nakhon Ratchasima Hospital, a tertiary care center in Northeast Thailand, from January 2015 to December 2019. The study was performed with approval from the Institutional Review Board. The inclusion criteria consist of patients who were diagnosed with asthma by a specialist (allergist or pulmonologist) who also had a history of stepping-down medications (having decreased one or more controllers). Additional inclusion criteria consist of those diagnosed with asthma in patients younger than 5 years, those with a history of recurrent wheezing that responds to bronchodilators on more than 3 occasions, patients with atopic diseases (such as allergic rhinitis, food allergy, atopic dermatitis) or family history of asthma.[1] Despite the contentious issue that children under the age of 5 are defined as having hyper-reactive airway disease as opposed to asthma, we decided to include these children due to the importance of symptom control in this patient group.

We excluded patients who could not be followed for up to 12 months after stepping-down treatment and patients who had a history of chronic lung disease, airway malformation, cardiovascular disease, and those who received systemic steroids for other conditions. Failure of stepping-down treatments was defined as the need for hospitalization, emergency department (ED) visit or an event found in the electronic medical records in which a patient had received nebulized bronchodilators or systemic steroids for asthma exacerbation within the 12 months following stepping-down treatment in a private clinic or hospital.

We recorded demographic data such as age, gender, age of asthma onset, address, weight, weight for height, presence of household smoking or pets, history of hospital admission, ED visits or intubation, skin prick test, pulmonary function test, controller medications, a dose of steroids, whether they have met a pharmacist, protocol of the medication step-down, and the season in which they initiated stepping-down treatment (in Thailand there are three seasons: rainy, winter, and summer). The duration of controlled symptoms was defined as the period of adequate symptom control without exacerbation.

Statistical analysis for comparison between the groups was made by the chi-squared test, Mann–Whitney U test, and Student's *t*-test. Results are reported as mean, standard deviation, median, and interquartile range. The hypothesis tests performed in all cases were bilateral, with a significance level of 0.05. Logistic regression analysis was used to determine factors associated with failure of stepping-down treatment; the results were described with an odds ratio, a 95% confidence interval (95% CI), and a *p*-value. The calculation for the time to failure of treatment was based on the start time of stepping-down until the onset of exacerbations. The risk of occurrence of failure for step-down over time was displayed using Kaplan–Meier curves by using Stata statistical software, version 16.

Results

The study cohort of 110 asthmatic patients who underwent stepping-down treatment was retrieved from electronic medical records of an allergy and chest clinic. Twenty patients were lost to follow-up before the 12 months. Of the 90 patients, 34 (37.8%) had asthma exacerbation during the 12 months. Most of these patients visited the ED. Five patients received hospitalization and three patients received systemic steroids. A sharp increase in cumulative events of asthma exacerbations was observed in the first half of the follow-up period (►**Fig. 1**).

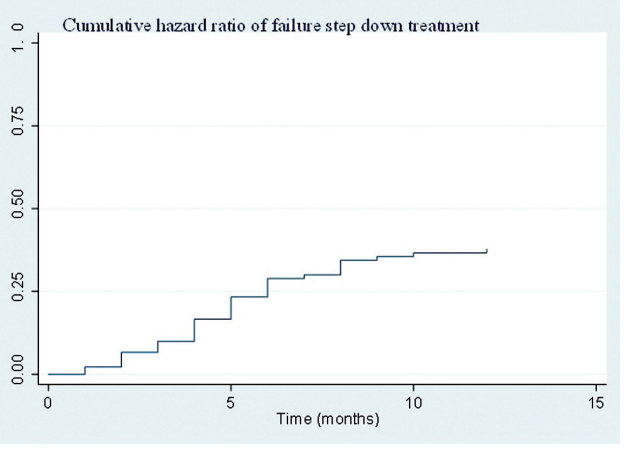

Fig. 1 Time to treatment failure after stepping down treatment.

Table 1 Demographics data between failure and success of stepping down treatment

Characteristics	Failure of stepping down treatment $n = 34$	Success of stepping down treatment $n = 56$	*p*-Value
Age (months), mean (SD)	79.3 (31.9)	84.9 (31.8)	0.421
Female, *n* (%)	12 (35.3)	20 (35.7)	1.000
Urban, *n* (%)	15 (44.1)	27 (48.2)	0.828
Obesity (weight for height > 140%), *n* (%)	8 (23.5)	9 (16.1)	0.414
Onset of asthma (months), median (IQR)	12 (9, 24)	24 (12, 36)	0.026[a]
Household smoking, *n* (%)	19 (55.9)	25 (44.6)	0.385
Having pets, *n* (%)	16 (61.5)	13 (48.2)	0.412
History intubation, *n* (%)	9 (26.5)	7 (12.5)	0.153
History hospitalization ≥3 times, *n* (%)	13 (38.2)	11 (19.6)	0.084
Met pharmacologist, *n* (%)	5 (14.7)	10 (17.9)	0.778
Comorbidity, *n* (%)	29 (85.3)	48 (85.7)	1.000
Dose of ICS (mcg), median (IQR)	400 (250,500)	400 (200,500)	0.465
LABA, *n* (%)	11 (32.4)	15 (26.8)	0.635
LTRA or theophylline, *n* (%)	15 (44.1)	19 (33.9)	0.375
Length of asthma stability < 9 months, *n* (%)	24 (70.6)	27 (48.2)	0.049[a]
Rainy season, *n* (%)	20 (58.8)	21 (37.5)	0.054
How to step down, *n* (%)			
Off LABA/LTRA	4 (11%)	8 (14%)	0.265
Decreased ICS	22 (64%)	37 (66%)	
Off ICS	3 (8.8%)	9 (16%)	
Decreased steroid and Off LABA/LTRA	5 (14%)	2 (3.5%)	

Abbreviations: ICS, inhaled corticosteroid; IQR, interquartile range; LABA, longed acting β2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
[a]$p < 0.05$.

The cumulative hazard ratio of patients with failure of stepping-down treatment was estimated using the Kaplan–Meier method.

►**Table 1** summarizes the characteristics of patients who failed or succeeded in stepping-down treatment. Younger age of onset and length of asthma stability of fewer than 9 months were significantly higher in the failure group ($p < 0.05$). The male-to-female ratio was 2:1; there was no statistical difference in age, obesity, household smoking, history of intubation, comorbidity (allergic rhinitis, obstructive sleep apnea, food allergy, and sinusitis), the dose of ICS, or protocol of stepping-down treatments between the two groups.

Regarding the use of controller medications, 71.1 (64 patients) and 28.9% (26 patients) were taking ICS or ICS-LABA (long-acting β-agonists), respectively. Other drugs such as leukotriene receptor antagonists or theophylline were used in 34 patients (37.8%) with no difference between the two groups. With regard to the seasonal factor in Thailand (summer, rainy, winter), we found an increased failure rate in stepping-down treatment during the rainy season without statistical significance.

We performed multiple logistic regression analyses of variables as listed in ►**Table 2** to find associated factors related to the failure of stepping-down asthma. The strongest predictor of failure was the length of asthma stability of fewer than 9 months before stepping-down treatment with an odds ratio of 4.79 (95% CI: 1.02–22.47). Other variables such as an age of onset at 12 months or younger, a history of three or more hospital admissions, obesity, and household smoking were trends to increase risk but were not statistically significant. There was no association between seasonal changes and failure of stepping-down treatment in this study.

►**Fig. 2** shows the time to treatment failure of the groups according to the length of asthma stability (< 9 months vs. at least 9 months).

Discussion

This study demonstrates that 37.8% of pediatric asthma participants in specialty clinics experienced a failure in stepping-down treatment. Compared with previous a study, 71.6% of patients stepping-down asthma medication were

Table 2 Factors associated with failure of stepping down treatment

Variables	Crude OR	Adjusted OR (95% CI)	*p*-Value	SE
Length of asthma stability < 9 months	2.58	4.79 (1.02–22.47)	0.047*	3.78
Onset of asthma ≤ 12 months	3.25	4.14 (0.97–17.79)	0.056	3.08
History admission ≥ 3 times	2.53	3.60 (0.83–15.6)	0.087	2.69
Obesity	1.35	3.74 (0.58–24.26)	0.167	3.57
In-house smoking	1.57	1.25 (0.29–5.35)	0.765	0.93
Rainy season	2.38	0.77 (0.18–3.30)	0.724	0.57

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SE, standard error.
*$p<0.05$.

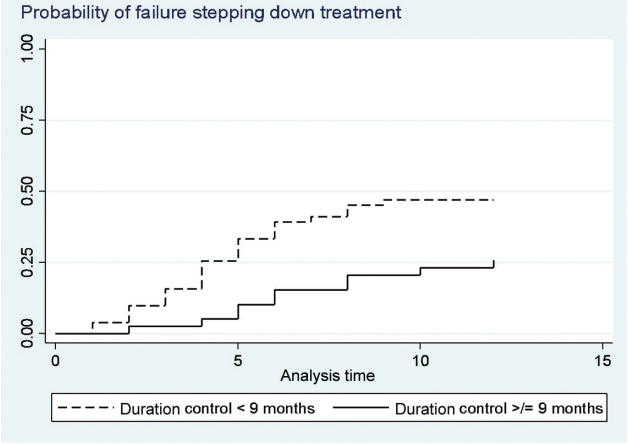

Fig. 2 Time to failure during stepping down treatment by using the Kaplan–Meier method on the basis of length of asthma stability before stepping down. Dot line: duration of control less than 9 months, solid line: duration of control more than or equal to 9 months.

successful after 3 months of follow-up.[13] Furthermore, 27.2% of asthmatic patients aged 12 years or older failed to stepping-down treatment in the 48 week-study.[15] In the 24-month period follow-up after stepping-down asthma medications, 32% of patients suffered asthma exacerbation.[14] A prospective multicenter study found 46.8% of patients experienced a loss of control after decreasing medication.[16] In that study, the loss of control was defined by events ranging from exacerbation, asthma control test score less than 19 or forced expiratory volume 1 (FEV1) decreased more than 20% from baseline.

The different failure rates in stepping-down treatment among studies could be due to varying definitions of treatment failure, length of follow-up, and differences among populations. This study shows a high failure rate of stepping-down treatment in children after a follow-up period of 12 months. Such findings may be explained by this study design that had a comparatively long follow-up period, coupled with the fact that our study population was inclusive of all severity levels of asthma. Furthermore, some patients in our study stopped ICS use during the follow-up period. A multicenter retrospective study on adults with moderate-severe asthma found that 41.7% failed in stepping-down treatment.[12] In adult studies, after cessation of low-dose ICS therapy in well-controlled asthma, almost 50% of patients had asthma exacerbation after 6 weeks of follow-up.[17,18] Furthermore, in a randomized, double-blinded, placebo-controlled trial in children aged between 5 and 18 years, 23% of patients with mild persistent asthma had treatment failure after stopping ICS.[19]

The early onset of asthma symptoms may be a factor associated with high failure rates of stepping-down treatment; the median onset of asthma was 12 to 24 months in our study. Some studies showed the timing of onset may be associated with subsequent asthma exacerbation. Children younger than 1 year who had onset of wheezing had a higher incidence of asthma exacerbation than patients who were older at the onset.[20] The early onset of wheezing in children is associated with decreased pulmonary function (FEV1/FVC) in adolescence compared with the late onset of childhood wheezing.[21]

Most patients in this study did not undergo pulmonary function tests or other investigations. Using only clinical judgment to stepping-down medications for patients in this study reflected the real-world practice in our asthma clinic. The approach of identifying guideline-eligible stepping-down patients such as the use of an Asthma Control Assessment questionnaire, pulmonary function test, and exhaled nitric oxide may increase the success rate.[13] In this study, almost 20% of the patients were lost to follow-up after stepping-down medications, while some patients stopped medications, mistaking their temporary symptom improvement as a remission. Techniques that encourage better adherence to treatment regimens could improve outcomes after stepping-down treatment.[22]

Many asthma guidelines suggest decreased medications after control of symptoms for longer than 3 months, but there is limited evidence to support this.[1,23] Similar to previous studies, our data suggest asthma cases that have shown stability for less than 9 months are associated with failure when attempting stepping-down treatment. Furthermore, our data also supported the notion that the duration of asthma stability before stepping-down treatment was associated with asthma outcomes, in particular to those who have had more than 6 months of asthma control.[12,15,23,24]

Seasonal effects such as spring, summer, and winter may increase the chances of successfully stepping-down treatment as opposed to during fall.[13] A previous study on asthmatic children aged between 1 and 5 years found that maintaining asthma control for at least 12 months before

stepping-down treatment increased the chances of success in stopping ICS, while stepping down during the rainy season decreased the success rate compared with the summer.[25] This study did not find an association between seasonal factors and the failure of stepping-down treatment. Furthermore, the data from this study does not support the notion that household smoking increases the risk of failure in stepping-down treatment, similar to a previous study.[14]

There are some limitations in this study, namely due to its retrospective study in the real-world setting, which results in some data being limited such as pulmonary function and skin prick tests and evaluation of compliance as many patients were lost to follow-up.

Stepping-down treatment in well-controlled pediatric asthma resulted in a high failure rate. The author suggests initiating stepping-down treatment in patients whose duration of asthma stability is greater than 9 months may improve the rate of success.

Conflict of Interest
None declared.

References

1 Global Initiative for Asthma Global strategy for asthma management and prevention 2022 [Internet]. [place unknown]: Global Initiative for Asthma; c2022 [cited 2022 Dec 3]. Accessed March 23, 2023 at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf
2 Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. J Asthma 2007;44(08):609–611
3 Rank MA, Liesinger JT, Branda ME, et al. Comparative safety and costs of stepping down asthma medications in patients with controlled asthma. J Allergy Clin Immunol 2016;137(05):1373–1379.e3
4 Loke YK, Blanco P, Thavarajah M, Wilson AM. Impact of Inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. PLoS One 2015;10(07):e0133428
5 Sannarangappa V, Jalleh R. Inhaled corticosteroids and secondary adrenal insufficiency. Open Respir Med J 2014;8:93–100
6 Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. Lancet Respir Med 2017;5(03):224–234
7 Wang AL, Datta S, Weiss ST, Tantisira KG. Remission of persistent childhood asthma: Early predictors of adult outcomes. J Allergy Clin Immunol 2019;143(05):1752–1759.e6
8 Bernstein JA, Mansfield L. Step-up and step-down treatments for optimal asthma control in children and adolescents. J Asthma 2019;56(07):758–770
9 Rogers L, Reibman J. Stepping down asthma treatment: how and when. Curr Opin Pulm Med 2012;18(01):70–75
10 Rank MA, Hagan JB, Park MA, 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 2013;131(03):724–729
11 Yamasaki A, Tomita K, Kato K, et al. Development and validation of a predictive model of failed stepping-down of inhaled corticosteroids in adult asthmatics. Patient Prefer Adherence 2016;10 (10):339–344
12 Martínez-Moragón E, Delgado J, Mogrovejo S, et al; en nombre del grupo de investigación STEP. ; Los autores quieren agradecer su colaboración a los siguientes investigadores participantes ordenados alfabéticamente. Factors that determine the loss of control when reducing therapy by steps in the treatment of moderate-severe asthma in standard clinical practice: a multicentre Spanish study. Rev Clin Esp (Barc) 2020;220(02):86–93
13 Rank MA, Branda ME, McWilliams DB, et al. Outcomes of stepping down asthma medications in a guideline-based pediatric asthma management program. Ann Allergy Asthma Immunol 2013;110 (05):354–358.e2
14 Rank MA, Johnson R, Branda M, et al. Long term outcomes after stepping down asthma controller medications: a claims-based, time-to-events analysis. Chest 2015;148(03):630–639
15 DiMango E, Rogers L, Reibman J, et al. Risk factors for asthma exacerbation and treatment failure in adults and adolescents with well-controlled asthma during continuation and step-down therapy. Ann Am Thorac Soc 2018;15(08):955–961
16 Pérez de Llano L, García-Rivero JL, Urrutia I, et al. A simple score for future risk prediction in patients with controlled asthma who undergo a guidelines-based step-down strategy. J Allergy Clin Immunol Pract 2019;7(04):1214–1221.e3
17 Koskela HO, Purokivi MK, Kokkarinen J. Stepping down from combination asthma therapy: The predictors of outcome. Respir Med 2016;117:109–115
18 Rank MA, Hagan JB, Park MA, 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 2013;131(03):724–729
19 Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 2011;377(9766):650–657
20 Mirabelli MC, Beavers SF, Chatterjee AB, Moorman JE. Age at asthma onset and subsequent asthma outcomes among adults with active asthma. Respir Med 2013;107(12):1829–1836
21 Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: a population-based birth cohort. J Allergy Clin Immunol 2016;138(04):1060–1070.e11
22 Price D, Chisholm A, Hillyer E, et al. Effect of inhaled corticosteroid therapy step down and dosing regimen on measures of asthma control. J Allergy Ther 2013;4:1–8
23 Chipps BE, Bacharier LB, Murphy KR, et al. The asthma controller step-down Yardstick. Ann Allergy Asthma Immunol 2019;122 (03):241–262.e4
24 Usmani OS, Kemppinen A, Gardener E, et al. A randomized pragmatic trial of changing to and stepping down fluticasone/formoterol in asthma. J Allergy Clin Immunol Pract 2017;5(05): 1378–1387.e5
25 Songmuang A, Chiyasong S, Waleekhachonloet O Patterns and Successful in Stopping Budesonide Inhaler Use in Asthmatic Patients Aged 1–5 years: A Retrospective Study [Internet]. SRIMEDJ 2017 [cited 2022 Apr. 9];32(6):571–8. Accessed March 23, 2023 at: https://li01.tci-thaijo.org/index.php/SRIMEDJ/article/view/106323