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.3,4 Inhaled corticosteroid (ICS) is the mainstay treatment in asthmatic children. Suppression of growth5 and the adrenal axis6 have been reported as adverse effects of ICS treatment. There are many studies...
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. 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. Additionally, it was found that stepping-down asthma medications in controlled patients can reduce treatment costs while suppressing asthma symptoms.

In studies of adults with asthma, a step down of ICS increased the risk of asthma exacerbation and the use of reliever medications. Predictors of failure in stepping-down treatment were the presence of comorbidities such as rhinitis, rhinosinusitis, the grade of phlegm, in addition to older age, and greater severity of asthma. In asthmatic children, decreased medication during the fall season is known to worsen the risk of failure in stepping-down treatment, in addition to shorter lengths of asthma stability related to more frequent exacerbations. 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. 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.
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 β2-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
after cessation of low-dose ICS therapy in well-controlled asthma. Medications, 32% of patients suffered asthma exacerbation in the 24-month period follow-up after stepping-down treatment in the 48 week-study. 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 medications, mistaking their temporary symptom relief for 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. In this study, almost 20% of the patients were lost to follow-up after stopping ICS. Moreover, 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.

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. 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.

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. In this study, almost 20% of the patients were lost to follow-up after stopping ICS. Moreover, our data also supported the notion that the duration of asthma stability before stepping-down treatment was associated with high failure rates of stepping-down treatment; patients 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. 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.

Table 2 Factors associated with failure of stepping-down treatment

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

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.
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
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