[1]Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy
[2]Internal Medicine Unit, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[3]Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy
[4]Department of Dermatology, Anna Meyer Children's University Hospital, Florence, Italy
[5]Pediatric Infectious Diseases Division, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy
Emails: f.mori@meyer.it; francymori@libero.it

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Asthma treatment patterns in Dutch children using medication dispensing data

To the Editor,

Asthma medicines (eg, inhaled corticosteroids [ICS] and inhaled β-agonists) are the most commonly chronically used medication in children.[1] In the Netherlands, asthma is treated according to a stepwise approach, which is mainly derived from the British Thoracic Society (BTS) guidelines.[2,3] The guidelines advice to start treatment at the most appropriate step according to clinical severity. Step-up of asthma treatment is advised if a child does not reach asthma control in the current step, and step down is advised if a child is well controlled for a period of 3 months.[2,4] Little is known about how well the stepwise approach in the guidelines is followed in clinical practice. Therefore, we studied patterns of asthma medication prescriptions in a large group of Dutch children and we focused on the patterns of step-up and step-down treatment.[2]

We retrospectively analyzed all prescriptions (from birth to date of pharmacy data extraction) dispensed for the treatment of asthma of 3573 children who were regular users of asthma medication. Children were recruited through community pharmacies (PACMAN cohort study). Children were invited to participate in the PACMAN cohort if they had used ≥3 prescriptions of asthma medication in last 2 years and ≥1 prescription in last 6 months, and were between 4 and 12 years of age. Records of dispensed asthma medication (between birth date and date of extraction) were extracted from the computerized pharmacy dispensing systems. In the Netherlands, individuals are usually registered at one pharmacy, which provides a full record of a patients' medication use.[5,6] Each dispensing of asthma medications (defined as asthma medications dispensed on the same date) was categorized according to the Dutch clinical asthma guidelines;[4] step 1: only short acting β-agonists (SABA) dispensed; step 2: monotherapy with low-dose inhaled corticosteroid (≤400 μg budesonide dipropionate (BDP) equivalent) or leukotriene modifier, with SABA if needed. Step 3: monotherapy with medium-dose inhaled corticosteroid (400-800 μg BDP equivalent) or combination therapy of low-dose inhaled corticosteroid (≤400 μg BDP equivalent) with a long-acting β-agonist or a leukotriene modifier and SABA if needed; step 4: monotherapy with high-dose inhaled corticosteroid (>800 μg BDP equivalent) or combination therapy of medium-dose inhaled corticosteroid (400-800 μg BDP equivalent) with a long-acting β-agonist or leukotriene modifier and SABA if needed; step 5: high-dose inhaled corticosteroid (>800 μg BDP equivalent) plus long-acting β-agonist with or without omalizumab and SABA if needed. Prescribing LABA without concomitant ICS is not recommended according to the guidelines. For a small part of the LABA prescriptions (2.65%), it was not clear whether single LABA prescriptions were added to existing medication or whether these were prescribed without other medication and therefore were

TABLE 1 Percentages of treatment changes per category of different initial treatment steps in 30 926 changes in 3573 children. [Colour table can be viewed at wileyonlinelibrary.com]

	Initial step					
	Step 0	Step 1	Step 2	Step 3	Step 4	Step 5
Next step	n=8442	n=9056	n=8711	n=3473	n=1137	n=107
Step 0		32.9	43.6	30.0	20.1	9.3
Step 1	37.6		36.2	33.0	30.2	24.3
Step 2	43.9	43.4		24.7	22.3	31.8
Step 3	13.2	14.9	11.4		18.4	14.0
Step 4	3.0	4.0	3.4	7.4		15.0
Step 5	0.1	0.3	0.4	0.3	1.8	
OCS	2.2	4.4	5.0	4.5	7.1	5.6
Total	100.0	100.0	100.0	100.0	100.0	100.0

OCS, oral corticosteroids.

Green: one step change (following guidelines), pink: two steps change (not following guidelines), red: more than two steps change (not following guidelines)

not following the guidelines. These prescriptions were excluded from the analyses. Generally, Dutch physicians prescribe chronic medications for 3-month periods, and therefore, if no asthma prescriptions were recorded for ≥6 months, we assumed the child did not use asthma medication at that time ("step 0"). Exacerbations are often treated with short course of oral corticosteroids (OCS). Therefore, a short course of OCS was categorized as a separate treatment step ("OCS"), outside the conventional treatment steps. We assessed whether a new dispensing of asthma medication would lead to a change in the current treatment step, whether there was a change in treatment steps, and whether this would be a change of 1 or more steps. Univariate logistic regression was used to assess which factors were associated with ≥1 step-up or down (not following guidelines). The following factors were studied: former treatment step, prescriber {GP vs related specialist (pediatricians, [pediatric] pulmonologist and [pediatric] internists)}, age of the child at the time of dispensing (younger or older of 4 years) and gender of the child.

In total, 61 127 asthma prescriptions were available of 3573 children. The mean age at the dates of dispensing of asthma medications was 6.0±3.1 years. The majority of the children in the study were boys (n=2240, 63.2%), and 65.9% of all prescriptions were for boys. The most frequent treatment step was step 2 (37.1% of prescriptions). In total, 9.2% (n=5641) of the prescriptions did not fit in a treatment step according to the guidelines (e.g., single LABA prescriptions (2.6%, n=1596) were dispensed or only systemic SABA). These prescriptions were excluded from the analysis, with 55 486 prescriptions remaining of which 80.6% were prescribed by GPs. In 9099 cases, a time gap >6 months between two following prescriptions was observed. Such a time gap was classified as treatment step 0 (a period without asthma treatment). In total, 30 926 changes in asthma treatment steps were observed.

Table 1 summarizes the proportion of the changes upon each treatment step. Overall, approximately half of the changes (50.4%) concerned one treatment step at a time; 45.5% of the changes concerned >1 treatment step at a time, while 4.1% of the asthma prescriptions were followed by prescription of an OCS. Children in step 1 had the highest chance (76.3%) to step up or down with one treatment step. In contrast, patients who were in higher treatment steps (steps 3-5) were more likely to step up or down with more than one treatment step at a time (63.3-79.4%). Older children (≥4 years) had a higher risk to change more than one step at a time compared to younger children (OR=1.5, *P* value <.01) and specialists more often adapted treatment more than one step at a time compared to GPs (OR=1.4, *P* value <.01). Gender of the child was not associated with changes >1 treatment step at a time (OR=1.0, *P* value >.1).

This is the first study to describe the clinical practice of the stepwise approach as described in international guidelines for asthma treatment. More than half of the asthma prescriptions in children of Dutch physicians are in line with these guidelines, changing asthma medication one step at a time. However, changes of two steps or more, which is not in line with guidelines regardless to clinical features, were also frequently observed. These larger steps were more likely prescribed by specialists (in comparison with GPs), in children that were already in higher treatment steps (steps 3-5), and in children that were older. This might reflect the higher volatility of asthma in the children with more severe disease. Because we do not have detailed clinical data of the children in this pharmacy database study, we chose our outcomes irrespective of clinical features (>1 step-up or down as "not following guidelines"). In clinical practice, physicians tend to make bigger steps in treatment changes in children at higher treatment levels, although the rationale for such a strategy is lacking in the literature. Future studies might answer the question whether a more differential approach in treatment steps between children with mild and more severe asthma may lead to improved outcomes and less side effects.

Ali Arabkhazaeli[1]
Susanne J. H. Vijverberg[1,2]
C. Kors van der Ent[3]
Jan A. M. Raaijmakers[1]
Anke H. Maitland-van der Zee[1,2]

[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
[2]Department of Respiratory Medicine, Academic Medical Center (AMC), University of Amsterdam (UvA), Amsterdam, The Netherlands
[3]Department of Pediatric Respiratory Medicine, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands
Email: a.h.maitland@amc.uva.nl

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Anaphylaxis to horses and epinephrine use: Increasing awareness among pediatric patients and families

To the Editor:

Pet allergens follow aeroallergens as a common cause of asthma and rhinitis in children.[1,2] Specifically, cat and dog dander are typical triggers of these symptoms.[1] However, high percent of patients with severe asthma can be sensitized to other mammals, such as horses and mice.[3] This is not limited to occupational or rural areas where exposure to this animal is more prevalent. A high rate of sensitization to horses in people with no known direct exposure who live in urban areas is well documented.[4] However, reports of anaphylaxis to furry animals are extremely rare, with only few cases reported in the literature. Despite the limited experience or reports with horse allergy and anaphylaxis, we have observed an increasing number of patients with the diagnosis of horse anaphylaxis in our hospital-based clinical practice.[1] Unfortunately, anaphylaxis is often misdiagnosed by patients and health providers due to lack of recognition of its signs and symptoms. This can carry serious consequences. Furthermore, the etiology of the anaphylaxis episode is often unknown, making prevention difficult. Herein, we report four male patients with an age range of 3-18 years who presented at our hospital with symptoms compatible with anaphylaxis to horses.

The first case, a previously healthy 3-year-old boy, with history of peanut and cashew anaphylaxis and dog allergy, was in a horse-drawn sleigh ride. Within minutes, he developed cough and wheezing and started to drool. He was treated with antihistamine and intramuscular steroid with resolution of symptoms. He had not eaten peanuts or tree nuts at least 2 hours prior the episode. Injectable epinephrine was not used during this event. His IgE/ImmunoCAP test results were strongly positive for horse dander, dog epithelium, and several tree nuts (Table 1).

The second case, an 8-year-old boy with history of allergy to dog and cat dander came to our clinic for initial evaluation. The patient visited a circus-type spectacle that involved horses. Within minutes of starting the show, he developed eye itchiness, facial urticaria, and swelling associated with shortness of breath and cough. He did not have an epinephrine autoinjector available. History was not indicative of anaphylaxis secondary to any kind of ingestion. IgE/ImmunoCAP was positive to horse dander (Table 1).

The third case, a 9-year-old man with history of allergy to cats, chicken feathers, and shrimp anaphylaxis visited a farm for the first time. Within minutes of visiting the horse barn, he developed

TABLE 1 Patient characteristics

Age (years)	Symptoms	Location of exposure to horses	Specific IgE (ImmunoCAP) to horse dander (kUnits/L)
3	Cough, drooling, wheezing, and itching	Horse-drawn sleigh hayride	19.8
8	Eye itchiness, shortness of breath, facial urticaria, and cough	Circus-type spectacle	2.04
9	Angioedema, shortness of breath	Visit to a farm	1.24
18	Angioedema and wheezing	Pet/horse therapy	30.3