Title page

Title: Subcutaneous immunotherapy: a perspective from Peking Union Medical College Hospital

Short title: Retrospective analysis of 5 years of SCIT

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Authorship

Yingyang Xu has made substantial contributions to design of the study, acquisition of data, analysis and interpretation of data, and drafting the article.

Kai Guan has made substantial contributions to design of the study, acquisition of data, and giving final approval of the version to be submitted.

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Abstract

Background

Allergen-specific immunotherapy (AIT) is the only disease-modifying treatment for IgE mediated disease. In china, AIT has been applied over 60 years and subcutaneous immunotherapy (SCIT) is the major route. This study analyzed the relatively comprehensive status of SCIT in our country.

Methods

Patients who initiated SCIT between January 1, 2015, and December 31, 2016 at Peking Union Medical College Hospital were collected and their medical records from January 1, 2015, to December 31, 2019 were obtained. The formulation and adherence of SCIT in different age groups and regions were analyzed.

Results

A total of 4731 patients receiving SCIT were analyzed, including 459 children (5-12 years), 624 adolescent (13-18 years) and 3648 adults. On a per-species allergen extract basis, multi-allergen SCIT were prescribed in 83% of patients. Mugwort, house dust mite and firebush were most frequently administered. On per-group allergen extract basis, 49% of SCIT were mixing formulations and weed pollen, tree pollen and house dust mite were most frequently used. The most common component of SCIT was mold in children (53%), whereas weed pollen in adolescents (59%) and adults (68%). Overall, 35% of patients completed at least 3-year SCIT. Children had the highest adherence of SCIT, followed by adolescents and adults (49%, 47% and 31%, respectively).

Conclusions

The majority of patients were prescribed SCIT of mixing formulation. Weed pollen was the most frequently used allergen group in SCIT, especially in Northern China. Real-life adherence in SCIT was still low which desiderate improvement of current procedure of SCIT.

Key words

adherence, allergen immunotherapy, subcutaneous immunotherapy

Background

Allergen-specific immunotherapy (AIT) has been widely accepted as the only treatment strategy for IgE mediated disease with disease-modifying effects. In addition to relieving allergic symptoms by reducing immune responses against specific allergens, AIT changes the course of allergic disease by inducing immune tolerance, preventing development of allergic comorbidities, reducing risk of asthma in allergic rhinitis patients, and preventing new allergen sensitization [1]. By administering allergen extracts using standardized methods, AIT can achieve long-term relief from the symptoms of allergen-associated diseases even after AIT termination. AIT has been used to treat patients with allergic diseases for 109 years, having first been used to treat hay fever in 1911 by Noon and Freeman [2,3]. Through the years, a large body of evidence has accumulated to document the efficacy and safety of AIT for treatment of allergic rhinitis, allergic asthma and venom allergy. Additionally, AIT has produced promising results in patients with atopic dermatitis [4,5] and IgE mediated food allergy [6,7]. Several routes of allergen delivery can be used in AIT. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the conventional routes of AIT in clinical practice. Novel AIT approaches, such as transdermal or epicutaneous immunotherapy [8] and intralymphatic immunotherapy [9], are under investigation.

The first allergy department in China was established in 1956 at Peking Union Medical College Hospital (PUMCH). Professor Ye and his colleagues at PUMCH, pioneers of AIT in China, used SCIT to treat allergic rhinitis and asthma starting in the 1960s. Because of differences in geography, climate, vegetation and living conditions, the spectrum of allergens in China differs compared with other countries. Thus, foreign allergen extracts are not suitable for Chinese patients. Ye et al. made a major contribution in identifying that weed pollens from *Artemisia* were the most important sources of allergens responsible for autumn pollinosis in Northern China. Subsequently, on the basis of research into common inhalant allergens in China, they started to prepare crude allergen extracts from pollen, house dust mite (HDM), fungi, and animal dander for skin tests and SCIT. Today, 30 types of crude allergen extracts are available for SCIT in China, all of which are produced by the Allergen Manufacturing and Research Center of PUMCH. Two standardized HDM allergen extracts, Novo-Helisen-Depot (Allergopharma Joachim Ganzer KG, Germany) and Alutard-SQ (ALK-Abelló, Denmark), have been approved for SCIT in China. Currently, SCIT is the major route for AIT in China; its clinical history is much longer than SLIT, which began to be administered starting in 2006. The only approved product for SLIT is Chanllergen-Df Drops (Wolwo Pharma, China), a standardized allergen extract from *Dermatophagoides farinae*. Another product for SLIT, an extract from *Artemisia annua*, is currently under evaluation in clinical trials [10].

Similarly to the implementation of AIT in the USA [11], AIT in China uses multiple relevant allergens for SCIT based on the clinical profile of each patient. Treatment lasts at least 3 years, which is one major reason for the high rate of SCIT discontinuation [12]. Many studies have examined the efficacy and safety of AIT. However, there is no literature describing the comprehensive status of AIT in China. Here, we retrospectively analyzed 5 years of data from patients receiving SCIT in our department and summarized the present status of SCIT in terms of the geographical distribution of allergens, the spectrum of multi-allergen SCIT, and the impact of SCIT adherence.

Methods

Study design

This was a single-center retrospective study. Patients who initiated SCIT between January 1, 2015, and December 31, 2016, at our center were enrolled. The medical records of patients receiving SCIT were obtained from the hospital international system (HIS) of PUMCH. To ensure the follow-up period covered at least 3 years for all patients, regular visits were tracked using the HIS until December 31, 2019. Thus, the overall analysis period was from January 1, 2015, to December 31, 2019. Information on SCIT, including formulation, course duration, adherence, and factors associated with adherence, was analyzed.

Datasets

The longitudinal data included age, sex, diagnosis, location of residence, dates of clinic visits, and SCIT information including prescriber, prescription date and formulation.

Patients

In accordance with national and international guidelines, patients diagnosed with allergic rhinoconjunctivitis (ARC), asthma, and atopic dermatitis caused by aeroallergens were prescribed SCIT. In addition to these three indications, a subset of patients in this study experienced other allergy-related disorders such as food allergy, anaphylaxis, eczema or urticaria. Patients who were prescribed SCIT against indications (i.e., for chronic urticaria) were excluded.

SCIT

Selection of allergen extracts for SCIT was performed on the basis of clinical history and the presence of specific IgE antibodies. Clinical history should support that symptoms are associated with exposure to allergens. The presence of specific IgE antibodies was determined by positive skin tests and/or IgE serology. Once clinically relevant allergens were identified in a patient, a mixture of allergen extracts could be formulated following the principle of mixed allergen immunotherapy [11]. The SCIT schedule includes dose escalation and a maintenance course. The duration should be at least 3 years; shorter durations were considered as discontinuation.

Allergen extracts for SCIT

At present, there are 14 types of aqueous allergen extracts frequently used in SCIT in

China: HDM (*Dermatophagoides farinae*), *Cladosporium herbarum*, *Alternaria alternata*, cypress, white ash, *Ailanthus altissima*, maple, mugwort (*Artemisia sieversiana*), ragweed, *Kochia scoparia*, *Humulus japonicus*, dog and cat dander, and cockroach. Additionally, nine allergen extract mixtures from multiple pollens, molds and house dust preparations are used for SCIT. Tree pollen extract mixtures include TP I (*Cryptomeria fortunei*, *Cunninghamia lanceolata*, *Populus deltoids*, *Ulmus pumila*, *Salix caprea*), TP II (*Betula verrucosa*, *Platanus acerifolia*, *Quercus alba*, *Juglans californica*, *Brassica campestris*) and TP III (*Morus alba*, *Ginkgo biloba*, *Spinacia oleracea*, *Typha angustifolia*). Weed pollen mixtures include WP I (*Helianthus annuus*, *anthium sibiricum*, *Chenopodium album*, *Cannabis sativa*) and WP II (*Zea mays*, *Sorghum vulgare*, *Scirpus planiculmis*, *Ricinus communis*). Poly-mold mixtures include PM I (*Penicillium chrysogenum*, *Aspergillus niger*, *Trichoderma koningii*, *Mucor racemosus*, *Rhizopus stolonifer*), PM II (*Stemphylium spp*., *Curvularia lunata*, *Claclosporium macrocarpum*, *Helminthosporium sorokinanum*, *Saccharomyces cerevisiae*) and PM III (*Ustilago maydis*, *Fusarium graminearum*, *Ustilago nuda*, *Cephalosporium*). All allergen extracts were produced by the Allergen Manufacturing and Research Center, PUMCH, Beijing, China.

Statistical analysis

All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). The Mann–Whitney and Kruskal–Wallis tests were used to assess differences in adherence and discontinuation rates by gender, age, location, primary disease/indication, and SCIT components. Values of $p < 0.05$ were considered statistically significant.

Ethics

This study was approved by the Research and Ethics Board of PUMCH (S-K1479).

Results

Demographic and clinical characteristics

Patient demographic and clinical characteristics are summarized in Table 1. A total of 4731 patients (2305 men) who initiated SCIT between January 1, 2015, and December 31, 2016, in our department were enrolled in the study. All SCIT prescriptions came from allergists. The age of SCIT initiation ranged from 7 to 85 years; 459 patients (10%) were children aged 5 to 12 years, 624 (13%) were adolescents aged 13 to 17 years, and the remainder (3648, 77%) were adults. Patients resided in all seven geographic regions of China. Most patients (3588, 70%) resided in Northern China where our hospital is located. The indications for SCIT included ARC (2856, 60%), ARC with cough or asthma (1823, 39%), and atopic dermatitis (52, 11%). Allergic comorbidities are shown in Table 1.

Formulation of SCIT

On the basis of type and source we classified allergen extracts into six groups: HDM including *D. farina* with or without house dust, mold, tree pollen (TP), weed pollen (WP), animal dander, and cockroach. We analyzed the components of SCIT prescriptions in terms of individual allergen extracts and allergen groups.

Single and mixed allergen extract components

Of a total of 4731 SCIT prescriptions, 2426 (51%) consisted of allergen extracts defined as a single group of components, whereas 2305 (49%) consisted of two or more groups of components (multi-group). The prescription frequencies of individual allergen extract groups are listed in Table 2. WP (65%), TP (38%) and HDM (36%) were the most frequently prescribed allergen extract groups overall. In approximately one third of cases, HDM (37%), WP (31%) and TP (39%) were prescribed as single group components of SCIT. In 41% of cases, animal dander was prescribed as a single group component of SCIT. In the majority of cases, TP (85%) and cockroach (89%) were used for mixed allergen SCIT.

The individual components of allergen extracts were further analyzed (Table 4). A total of 824 patients (17%) were administered single allergen extracts and 83% were used multi-allergen extracts for SCIT. Overall, mugwort (2559, 54%), HDM (1696, 36%) and firebush (1633, 35%) were the most frequently prescribed allergen extracts. Among

patients receiving single allergen extract SCIT, 624 (75.7%) received HDM extract, 53 (6.4%) received mugwort extract, and 46 (5.5%) received cypress extract.

Components of SCIT in different age groups

Among children, mold was the most frequently prescribed allergen group for SCIT (53%), followed by WP (48%) and HDM (44%). Among adolescents, the most frequently prescribed allergen groups were WP (59%), mold (45%) and HDM (44%). Among adults, WP was the most frequently prescribed allergen group (68%) followed by TP (40%) and HDM (33%). The spectrum of components used in each age group is illustrated in Figure 1a.

Components of SCIT in different geographic regions

In Northwest and North China, the most frequently prescribed allergen extracts were WP, TP, and HDM. In East, Central, and Southwest China, the most frequently prescribed allergen extracts were HDM, WP and mold. The most frequently prescribed allergen extracts were WP, HDM and TP in Northeast China, and HDM, WP and TP in Southern China. The spectrum of SCIT components prescribed in different regions is shown in Figure 1b.

Components of SCIT by diseases/indications

In this study, there were three primary indications for SCIT: ARC without asthma, ARC with cough or asthma, and atopic dermatitis. The components of SCIT for different indications are shown in Table 2. Roughly half (53%, 47% and 46%, respectively) of patients receiving SCIT with mold, animal dander and HDM extract were diagnosed with ARC with cough or asthma. Roughly one third (35% and 31%, respectively) of patients receiving SCIT with WP and TP extract were diagnosed with ARC with cough or asthma. The majority (41 of 52) of patients with atopic dermatitis were treated with HDM extract.

Adherence to SCIT

Overall, 1651 of 4731 patients (35%) received continuous SCIT for at least 3 years. The discontinuation rates were 34%, 18%, 13%, 28% and 7%, respectively, by the end of the first, second, third, fourth and fifth treatment year (Figure 2a). Excluding

discontinuation times beyond 3 years, the median time to discontinuation was 12 months.

Children aged 5 to 12 years had the highest adherence rates, followed by adolescents aged 13 to 17 years and then by adults (49%, 47% and 31%, respectively; Figure 2b). Adherence rates were significantly different among the three age groups ($p<0.0001$). SCIT adherence rates also differed significantly among patients with different primary allergic diseases ($p<0.002$). Compared with other primary diseases, patients with ARC and asthma had the highest adherence rates (460/1100, 41.8%). The adherence rates of male showed better performance than female ($p=0.04$). No differences in adherence rates were observed by geographic region of residence or by type of SCIT (single or multi-group allergen extracts). Factors associated with SCIT adherence are summarized in Table 3.

Discussion

This study provided an overview of the status of SCIT in PUMCH. We focused not only on HDM SCIT, which has been reported previously, but also on SCIT with pollen, mold, and mixed allergen extracts. Over a period of 5 years, data from 4731 patients receiving SCIT in PUMCH were collected and analyzed. We cannot hope to fully capture the status of SCIT in all of China using a single center study. However, we believe that our results reflect one part of the current status of SCIT, especially in Northern China. We base this judgement on the large number of out-patients in our department, the full accessibility of allergen extracts for SCIT, and the high social influence of our department.

Most patients receiving SCIT were adults (77%), while 10% were children and 13% were adolescents. Several factors contributed to the age distribution of SCIT patients. According to a survey conducted in 18 major cities across China, the mean prevalence of self-reported allergic rhinitis in adults was 17.6% [13]. By contrast, the mean prevalence of allergic rhinitis in children aged 6 to 13 years was 9.8% in 8 metropolitan cities across China [14]. However, 79% of the total Chinese population are adults whereas children and adolescents account for only 21% (data from The Census of China, 2010).

Thus, it was expected that the number of adults with allergic rhinitis would be significantly higher than the number of children and adolescents. Additionally, SCIT may be prescribed more frequently in adults compared with younger age groups. Most patients in our department were adults. Although children and adolescents were also sent for consultation in our department, they may be more likely to visit a children's hospital. If true, this might result in some degree of age bias.

In the general population, polysensitization is more common than monosensitization [15-18]. Additionally, 60% to 80% of patients consulting allergists were polysensitized, with two or more relevant causal allergens identified [17-21]. It remains a controversial issue whether allergen extracts can be mixed for SCIT. The AIT practice guidelines of the American Academy of Allergy, Asthma and Immunology favor mixing allergen extracts following certain principles [11]. By contrast, it was recommended not to mix non-homologues allergen extracts for SCIT in Europe [22]. In China, mixing allergen extracts is preferred for SCIT in polysensitized patients. In our practice, half of SCIT is prescribed on a per-group allergen extract basis and 83% is prescribed on a per-species allergen extract basis were mixing formulations. Compared with single allergen extracts, SCIT with mixtures of extracts avoids the need for multiple injections and reduces the cost and time required of patients. This could potentially increase compliance and the number of patients who complete full courses of SCIT.

The geoepidemiology of inhalant allergens varies regionally. Generally, allergies to pollen, mold, HDM, insects and animal dander are the most common allergens. Based on skin prick tests, studies from East and Central China demonstrated that HDM was the most common inhalant allergen in adults with allergic rhinitis [17,23-26], whereas data from North and Northwest China suggested that *Artemisia*, *Chenopodium* and lupulus were the most common allergens [18,27]. From a treatment perspective, WP, TP and HDM were the most prevalent groups of allergen extracts used for SCIT in the patients studied here. In terms of per-species allergen extracts, mugwort, HDM, firebush, Japanese hops and ragweed extracts had the highest prescription rates. The administration frequency of mugwort extract was much higher than other extracts (Table 4). This finding might be associated with the residence of studied subjects (82% in Northern China). Because

of its climate and environmental conditions, seasonal pollen exposure is very high in Northern China [18]. In agreement with a previous study [17], *Alternaria tenuis*, HDM and mugwort were the primary allergen extracts used for SCIT in children and adolescents. In adults, mugwort, firebush and HDM extract were the most prescribed allergens for SCIT. Considering the primary allergic diseases driving patients to initiate SCIT, we found that more patients treated with mold, animal dander and HDM extract suffered from cough or asthma, whereas those treated with WP and TP were more likely to present with ARC only. It is important to analyze patterns of frequently prescribed allergens in different regions, different age groups and different allergic diseases. This knowledge could help physicians to efficiently identify relevant allergens in patients undergoing SCIT. Because SCIT for allergy is relatively new and is still developing, understanding these patterns may also be informative for hospitals planning to establish allergy departments providing SCIT.

Overall adherence to SCIT in our department was 35% at the completion of the third year. Children showed the highest adherence, followed by adolescents and then adults. Our findings were identical to those of a German study [12], although adherence to SCIT was much lower in the Netherlands (23%). Compared with female patients and those with ARC only, male patients and patients with ARC and asthma showed better adherence. Completion of SCIT is necessary for treatment efficacy. However, owing to its high costs in time and expense, adherence and compliance are not satisfactory in patients receiving SCIT. The procedure for SCIT is complex and requires patients to visit doctors regularly and continually. At present, SCIT is not reimbursed by health insurance in China. Thus, an optimized procedure is urgently needed. Rush and cluster immunotherapy are under evaluation for this purpose and the initial results have been promising. We hope additional encouraging advances are made in the near future.

In conclusion, the data from this single center study showed that the majority of patients were prescribed multi-allergen extracts for SCIT. Overall, WP was the most commonly administered allergen group in SCIT, and the most frequently prescribed allergens were mugwort, HDM, and firebush. Only 35% of patients completed at least 3 years of SCIT,

and children exhibited the highest adherence rates.

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Figure legends

Figure 1a. Distribution of allergen extract components in SCIT prescription in different age groups. SCIT: subcutaneous immunotherapy.

Figure 1b. Distribution of allergen extract components in SCIT prescription in different geographic regions. SCIT: subcutaneous immunotherapy.

Figure 2a. Discontinuation rates by the end of different treat years.

Figure 2b. Adherence and discontinuation in different age groups

Table 1 Demographic and clinical characteristics of studied patients

		Whole patients		Children		Adolescents		Adults	
Total		4731		459		624		3648	
gender	male	2305	52.7%	312	68.0%	458	73.4%	1535	42.1%
	female	2426	55.5%	147	32.0%	166	26.6%	2113	57.9%
Geographic distribution	northwest	136	3.1%	19	4.1%	18	2.9%	99	2.7%
	north	3588	82.1%	324	70.6%	445	71.3%	2819	77.3%
	east	347	7.9%	38	8.3%	65	10.4%	244	6.7%
	central	155	3.5%	19	4.1%	18	2.9%	118	3.2%
	south	18	0.4%	3	0.7%	3	0.5%	12	0.3%
	southwest	34	0.7%	5	1.1%	5	0.8%	24	0.7%
Primary diseases	allergic rhinoconjunctivitis	2781	58.8%	236	51.4%	323	51.8%	2222	60.9%
	allergic rhinoconjunctivitis combined with asthma	1100	23.3%	105	22.9%	165	26.4%	830	22.8%
	allergic rhinoconjunctivitis combined with cough	129	2.7%	31	6.8%	15	2.4%	83	2.3%
	allergic rhinoconjunctivitis combined with food allergy and/ or anaphylaxis	53	1.1%	1	0.2%	1	0.2%	51	1.4%
	allergic rhinoconjunctivitis	10	0.2%	4	0.9%	2	0.3%	4	0.1%

combined with eczema or atopic dermatitis								
allergic rhinoconjunctivitis	12	0.3%	0	0.0%	1	0.2%	11	0.3%
combined with urticaria								
asthma	594	12.6%	71	15.5%	105	16.8%	418	11.5%
atopic dermatitis	52	1.1%	11	2.4%	12	1.9%	29	0.8%

Table 2 Allergen extracts components in SCIT prescription

Allergen groups	HDM		Mold		Weed pollen		Tree pollen		Animal dander		cockroach	
Total	1696	36%	803	17%	3068	65%	1793	38%	203	4%	87	2%
Single group	624	37%	251	31%	1184	39%	274	15%	83	41%	10	11%
Multi group	1072	63%	552	69%	1884	61%	1519	85%	120	59%	77	89%
Distribution of prescription components distribution in different age groups												
5-12 years	201	44%	242	53%	221	48%	127	28%	5	1%	1	0%
13-17 years	274	44%	280	45%	369	59%	191	31%	9	1%	7	1%
≥18 years	1221	33%	281	8%	2478	68%	1475	40%	189	5%	79	2%
Distribution of prescription components distribution in different geographic regions												
northeast	204	45%	57	13%	301	66%	159	35%	14	3%	3	1%
northwest	28	21%	18	13%	115	85%	46	34%	3	2%	1	1%
north	1124	31%	570	16%	2418	67%	1454	41%	167	5%	64	2%
east	202	58%	108	31%	160	46%	87	25%	13	4%	9	3%
central	108	70%	37	24%	56	36%	34	22%	2	1%	6	4%
south	8	44%	4	22%	7	39%	5	28%	3	17%	2	11%
southwest	22	65%	9	26%	11	32%	8	24%	1	3%	2	6%
Distribution of prescription components distribution for different indications												
ARC without asthma	869	51%	356	44%	1992	65%	1230	69%	107	53%	52	60%
ARC with cough or asthma	786	46%	429	53%	1067	35%	556	31%	96	47%	34	39%
Atopic dermatitis	41	2%	18	2%	9	0%	7	0%	0	0%	1	1%

Table 3 Adherence and discontinuation of SCIT

	continuous treatment	adjusted residuals	discontinuous treatment	adjusted residuals
Gender				
male	838	(2.1)	1467	(2.1)
female	813	(-2.1)	1613	(-2.1)
Age groups				
children	227	(6.9)	232	(-6.9)
adolescents	294	(6.9)	330	(-6.9)
adults	1130	(10.4)	2518	(-10.4)
Geographic distribution				
northeast	157	-0.1	296	0.1
northwest	35	-2.3	101	2.3
north	1267	1.1	2321	-1.1
east	123	0.2	224	-0.2
central	56	0.3	99	-0.3
south	7	0.4	11	-0.4
southwest	6	-2.1	28	2.1
Primary diseases				
allergic rhinoconjunctivitis	924	-2.9	1857	2.9
allergic rhinoconjunctivitis combined with asthma	460	5.5	640	-5.5
allergic rhinoconjunctivitis combined with cough	52	1.3	77	-1.3
allergic rhinoconjunctivitis combined with food allergy and/ or anaphylaxis	17	-0.4	36	0.4
allergic rhinoconjunctivitis combined with eczema or atopic dermatitis	3	-0.3	7	0.3

allergic rhinoconjunctivitis combined with urticaria	1	-1.9	11	1.9
asthma	179	-2.6	415	2.6
atopic dermatitis	15	-0.9	37	0.9

Table 4 Prescription number for individual allergen extracts in different groups of patients

	total	5-12 years	13-17 years	⩾18 years	northeast	northwest	north	east	central	south	southwest
Artemisia	2559	192	299	2068	267	102	2022	112	42	7	7
Dermatophagoides farinae	1696	201	274	1221	204	28	1124	202	108	8	22
Kochia scoparia	1633	123	200	1310	148	61	1316	70	29	5	4
Humulus japonicus	1295	95	161	1039	100	33	1060	63	32	3	4
Ambrosia	746	84	97	565	100	28	568	35	13	1	1
Alternaria tenuis	739	236	274	229	53	14	528	99	35	2	8
Cypress	691	41	63	587	27	5	626	20	6	2	5
Firmiana	628	60	95	473	40	27	498	42	18	3	0
White ash	431	39	67	325	29	20	353	16	12	0	1
Cladosporium herbarum	251	73	84	94	15	11	161	39	17	3	5
Dog	125	2	5	118	9	0	104	9	0	2	1
Cat	115	3	6	106	6	3	95	7	2	1	1
Cockroach	87	1	7	79	3	1	64	9	6	2	2
Ailanthus altissima	77	8	19	50	9	3	64	1	0	0	0

Figure 1a

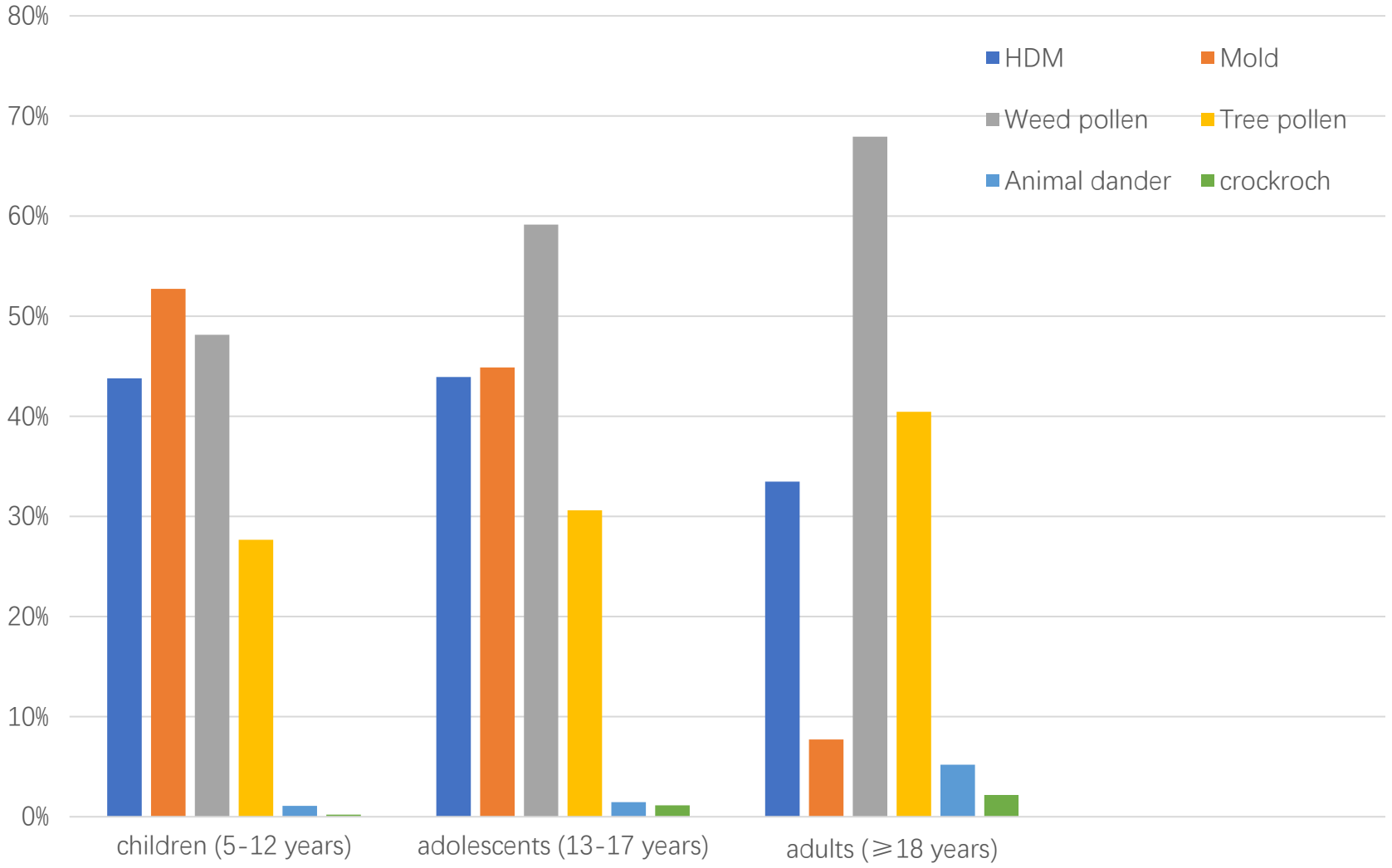

80%
70%
60%
50%
40%
30%
20%
10%
0%
HDM
Mold
Weed pollen
Tree pollen
Animal dander
crockroch
children (5-12 years)
adolescents (13-17 years)
adults (⩾18 years)

Figure 1b

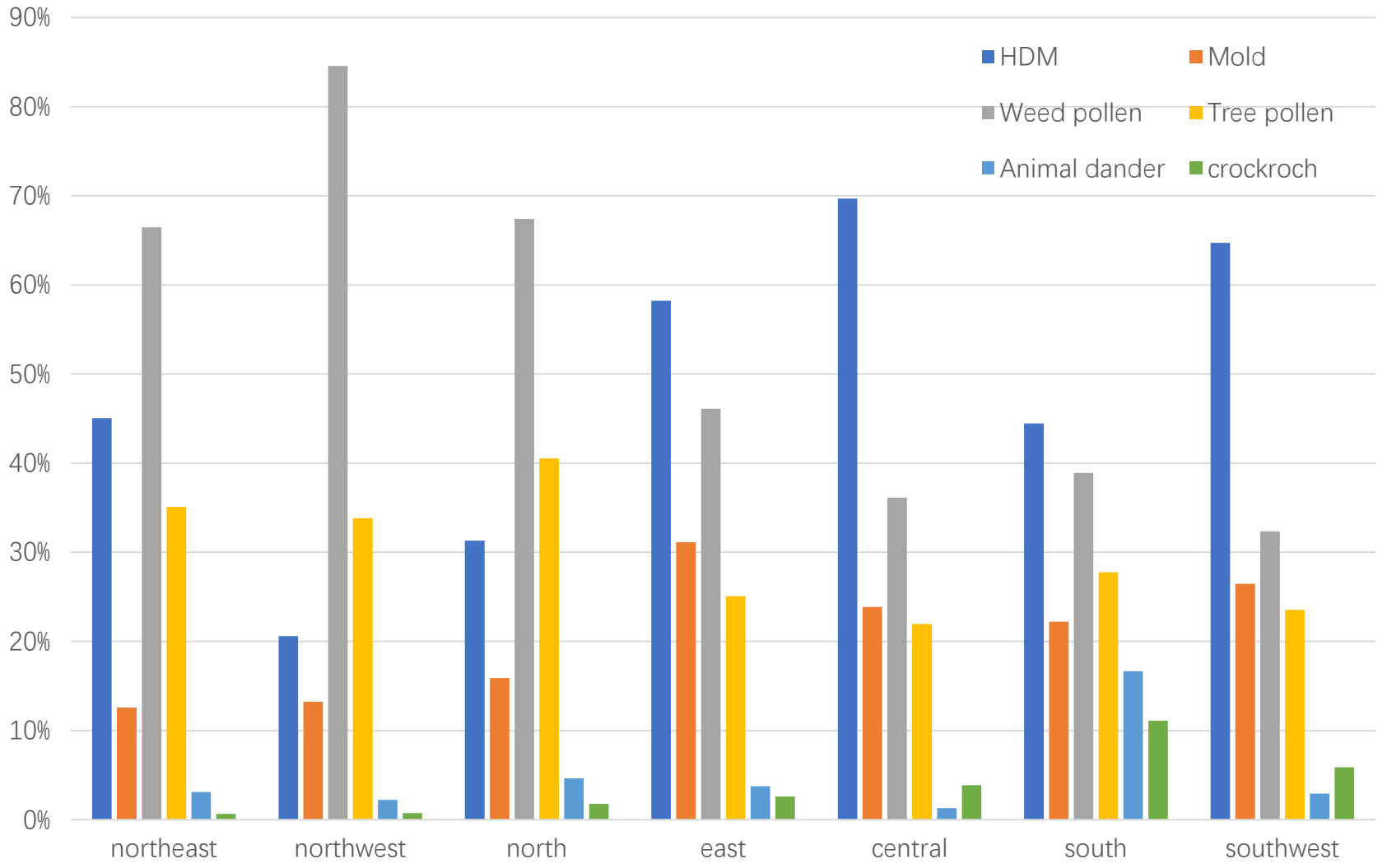

90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
HDM
Mold
Weed pollen
Tree pollen
Animal dander
crockroch
northeast
northwest
north
east
central
south
southwest

Figure 2a

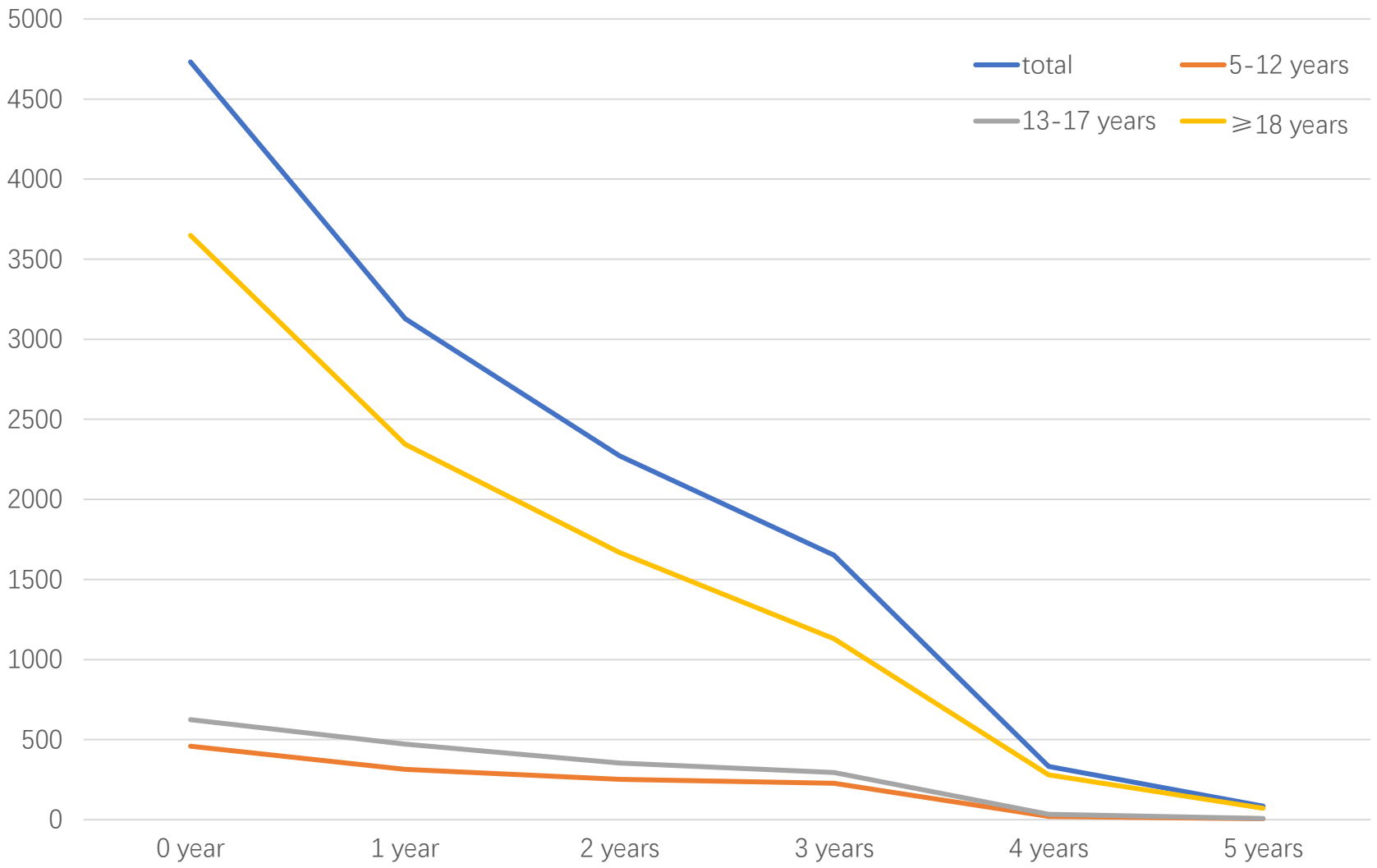
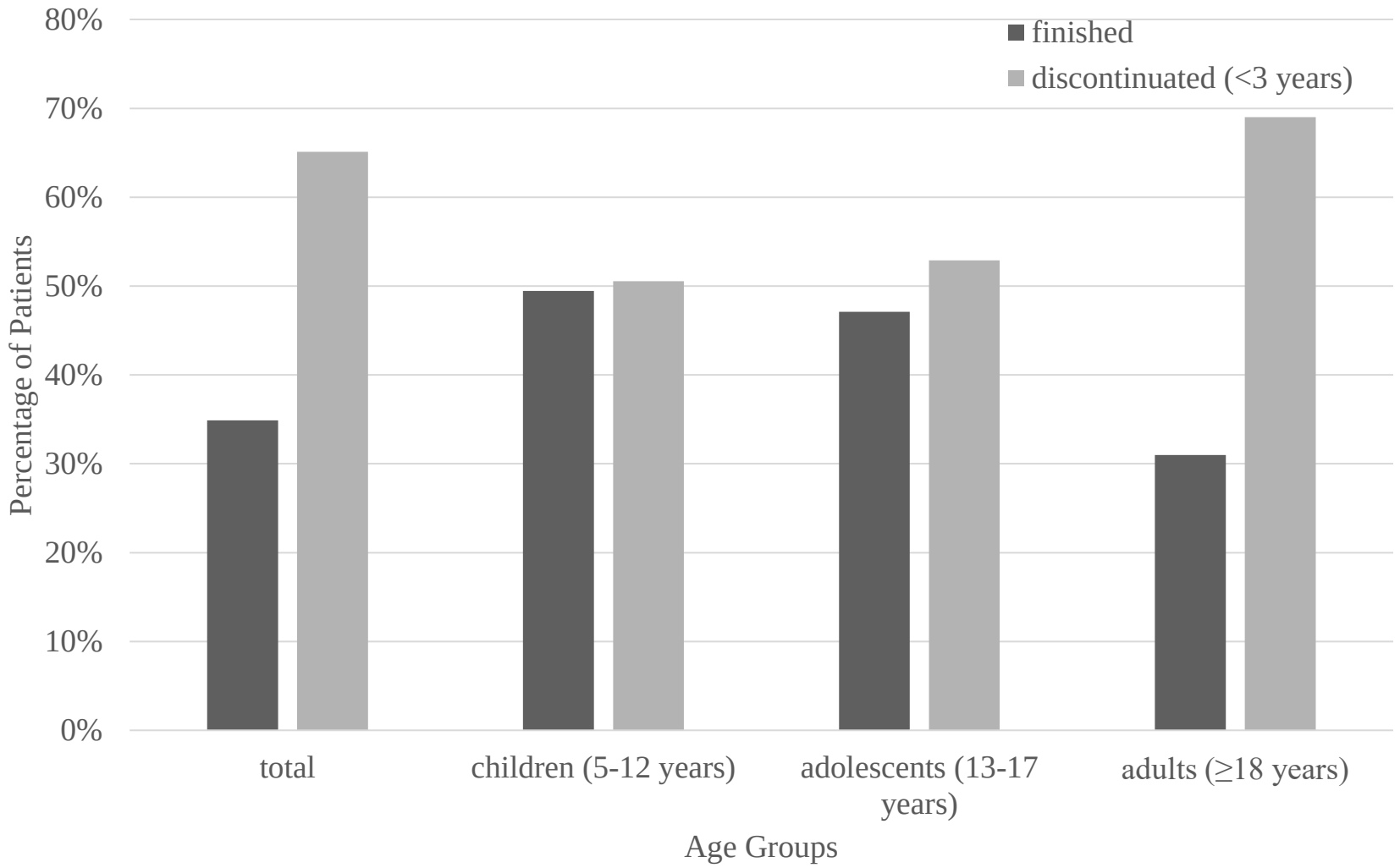

5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0 year
1 year
2 years
3 years
4 years
5 years
total
5-12 years
13-17 years
⩾18 years

Figure 2b


80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Patients
finished
discontinuated (<3 years)
total
children (5-12 years)
adolescents (13-17 years)
adults (≥18 years)
Age Groups