

Patterns of allergen sensitization in patients with severe asthma in Germany

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Clinical Implications

- In our analyses, the level of allergen sensitization was unexpectedly high, with more than 70% sensitized to at least 1 allergen. This confirms recent recommendations that allergy testing should form a standard part of the management of severe asthma.

TO THE EDITOR:

Allergen sensitization tests in severe asthma should include the most common allergens to reduce the chance of false negative results. However, we currently do not know which allergen sensitizations, demonstrated by elevated allergen-specific IgE (sIgE), are common in German adults, and as a consequence there is variability in testing between centers. In one analysis of 362 patients with severe asthma and previously negative sIgE (thus diagnosed as nonatopic asthma), more than half of the patients demonstrated at least 1 perennial aeroallergen sensitization in a subsequent 35 allergen sIgE test.¹ We therefore conducted a prospective multicenter study to collect sIgE from adults with severe asthma recruited throughout Germany, as the first step to develop a standardized panel. Although data from 37 children and adolescents were also collected, because of a small sample size their data are not included in these analyses.

We initially conducted online screening using a questionnaire to identify patients with severe, uncontrolled asthma. They were contacted by a call center to confirm interest in participation. All potentially suitable individuals were then referred to an investigator, who, after the individual had provided informed consent, confirmed the presence of severe, uncontrolled disease (symptoms despite Global Initiative for Asthma Step IV medication²).

Given the intention to measure sIgE levels, we excluded individuals receiving omalizumab from the study. Blood samples were collected for extended serological testing to 26 perennial allergens, 5 mixes of perennial allergens, and 8 seasonal allergens (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), with both total IgE and sIgE levels determined (ImmunoCap; Thermo Fisher Scientific, Uppsala, Sweden). Sensitization to an allergen was defined as sIgE >0.35 kU/L. Further details of the methods are available in this article's Online Repository at www.jaci-inpractice.org.

Of 35,586 adults screened in the online tool between April 2016 and February 2017, 11,084 had asthma, and so were asked to complete the online questionnaire; 5343 agreed to take part in the study, 1164 of whom provided contact details and so were contacted by the call center, with 374 who met the criteria for the presence of severe, uncontrolled asthma then attending a study visit. Eighteen individuals were excluded by the investigators as not actually meeting criteria for severe, uncontrolled asthma, so the population analyzed totaled 356, all of whom completed all assessments. The majority were female and non- or ex-smokers, and had been diagnosed in adulthood (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Median total IgE within the 356 individuals was 101.0 kU/L (interquartile range, 58.8-325.0 kU/L). Importantly, despite most having been diagnosed with asthma in adulthood, the proportion of sensitized individuals was high, with over a fifth sensitized to more than 10 allergens, and only a quarter of the individuals not sensitized to any of the allergens included in the panel (Table I). Furthermore, more than 60% were sensitized to at least 1 perennial allergen, and more than 50% were sensitized to at least 1 seasonal allergen.

The most common individual allergens to which individuals were sensitized were the major pollen allergens Phl p 1 and Phl p 5 (g213 [mix]) from timothy grass and Bet v 1 (t215) from birch, and the mammalian allergens cat (e1) and dog (e5) (Figure 1 and Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The median sIgE in these 4 groups was between 3.5 and 6 kU/L, indicating high levels. However, as shown in the violin plots, there was high variability around this median,

TABLE I. Number (%) of adults with sensitizations to the tested allergens

Category	No. of sensitizations	Individuals, n (%) N = 356
All sensitizations (excluding CCD marker)	0	99 (27.8)
	1-4	95 (26.7)
	5-10	85 (23.9)
	>10	77 (21.6)
Sensitization to perennial allergen sources	0	140 (39.3)
	1-4	67 (18.8)
	5-10	86 (24.2)
	>10	63 (17.7)
Sensitization to seasonal allergen sources*	0	176 (49.4)
	1-4	176 (49.4)
	5-8	4 (1.1)
Sensitization only to seasonal allergen (and not to any perennial allergen)		41 (11.5)

CCD, Cross-reactive carbohydrate determinant.

*Only 8 seasonal allergens (single allergens, combinations, or extracts) were tested.

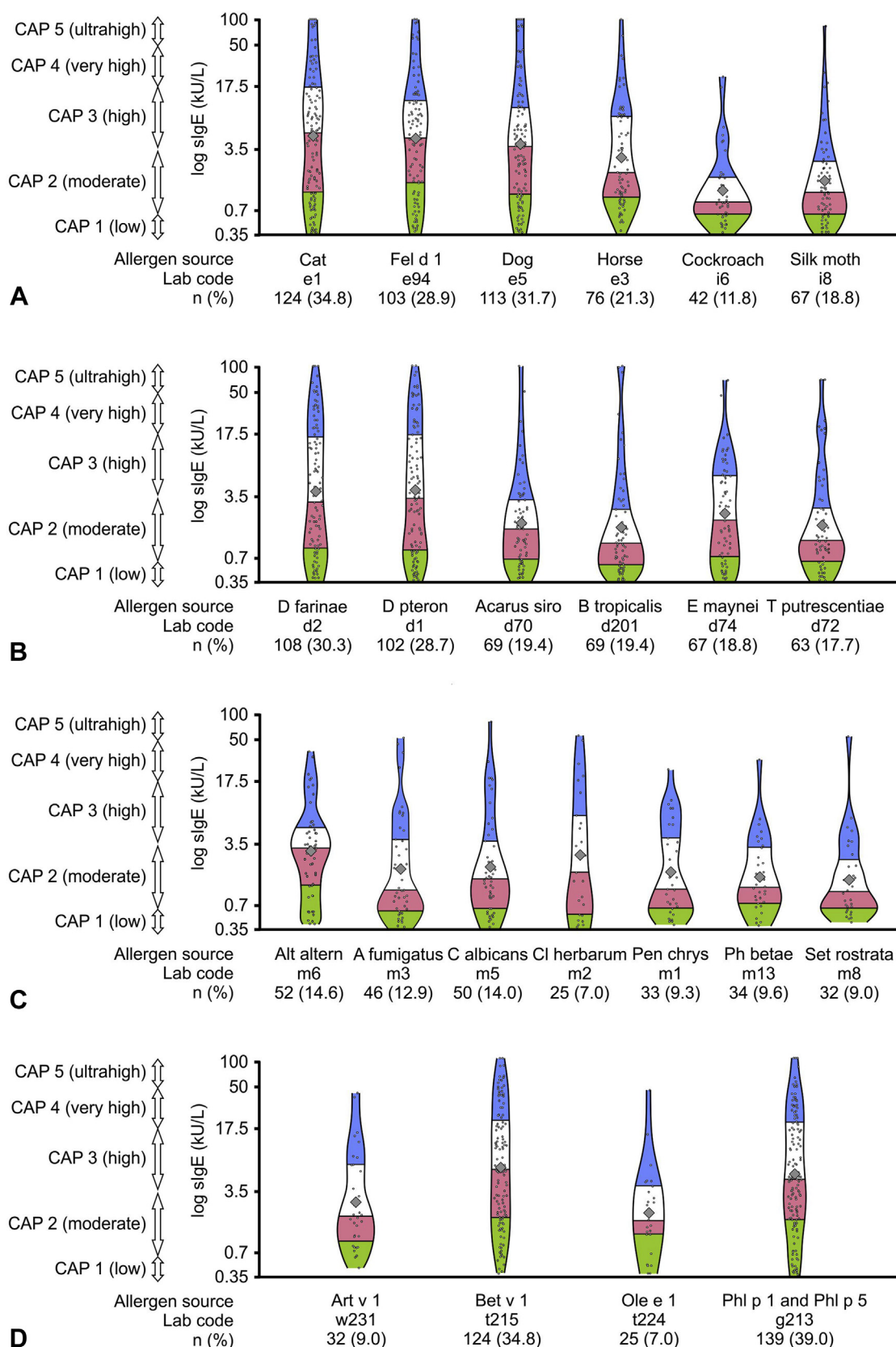


FIGURE 1. Violin plots representing number (≥ 20) of sensitized adults with each level of sIgE for **(A)** mammalian and insect allergens; **(B)** house dust and storage mites; **(C)** mold/microorganism; and **(D)** pollen allergens. Less prevalent sensitizations (sIgE in $n < 20$) are depicted in [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org). Only patients with sIgE > 0.35 kU/L (indicating sensitization) are displayed. sIgE, Specific IgE.

from low to ultrahigh. Many of the allergens had 1 or 2 distinct nodes; although for most the widest node (indicating the greatest number of individuals) was at low or moderate sIgE, in patients sensitized to cat and dog dander and to the cat major allergen Fel d 1, the most common level of sIgE was high.

Overall, therefore, in the studied population of individuals with severe, uncontrolled asthma, allergic IgE sensitizations were common. Because the population that we recruited had predominantly adult-onset asthma, this is somewhat unexpected, given that the allergic asthma phenotype is considered to typically be early onset.³ However, the results are consistent with a previous study, in which 73%, 61%, and 41% of patients ≤ 35 , 36 to 59, and ≥ 60 years old, respectively, were sensitized to at least 1 indoor allergen.⁴

We recognize that our analyses have some weaknesses. First, we did not perform skin prick tests to confirm functional reactivity to allergens. Previous and current studies demonstrated moderate qualitative concordance but poor quantitative correlations between sIgE and skin test reactivity.^{5,6} Secondly, we excluded individuals currently receiving omalizumab. This was for obvious reasons, because this might create a bias as omalizumab binds to IgE, extending the half-life, so providing artificially high total IgE and sIgE levels.⁷ However, this excluded only 1% of the screened population. Furthermore, the study was conducted over 11 months. This makes the seasonal allergen data difficult to interpret—an individual who was sensitized only to a seasonal allergen may have been excluded from the study if he or she was screened during the winter (due to a lack of symptoms). It is possible, therefore, that such individuals are underrepresented in our analysis. In addition, sensitization does not necessarily mean an individual will experience symptoms on exposure to the positively tested allergens.^{2,8} Finally, even though more than 11,000 people completed the initial survey, the final analysis was only on 356 patients (approximately 3%), with no information collected on race or ethnicity. Although this 3% is consistent with estimates of the prevalence of severe asthma,⁹ we acknowledge that the results may not be generalizable to other populations, especially given that the study was conducted in Germany.

In summary, we clearly demonstrated that, in a population of adults with severe, uncontrolled asthma, IgE-sensitization is surprisingly common, with the majority of individuals sensitized to multiple atopic allergens, representing a broad sIgE repertoire. Pollen and pet allergens were most prevalent, resulting in many individuals exhibiting high levels of sIgE, although with very high variability across the population studied. This indicates the importance of IgE-mediated allergies (both to perennial and seasonal allergens) in severe asthma, and the necessity for allergy testing (as recommended in guidelines^{2,9}).

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Conflicts of interest: J. Kleine-Tebbe declares lecture fees from Allergopharma, ALK-Abelló, AstraZeneca, Bencard, Dr. Pflieger, HAL Allergy, Leti, Lofarma, Novartis, Stallergenes-Greer, and ThermoFisher; industry-sponsored grants to his institution from Allergopharma, ALK-Abelló, HAL Allergy, GlaxoSmithKline, LETI, Novartis, Parexel International, and Stallergenes-Greer; and consultancy fees from Allergen Online (in support of an allergen database), Allergy Therapeutics, Bencard, ALK-Abelló, Circassia, LETI, Lofarma, Merck (US), Novartis, Paul-Ehrlich-Institute (EMA), and the World Health Organization/International Union of Immunological Societies Allergen Nomenclature Sub-committee. C. Mailänder is an employee of Novartis Pharma GmbH, the sponsor of the study.

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ONLINE REPOSITORY

PATIENT SELECTION AND RECRUITMENT

Potential participants in the study were recruited via online advertisements. These directed individuals to an online questionnaire, with no restrictions applied in terms of patient selection. This questionnaire was developed for this study, and included 24 questions to identify patients who had severe, uncontrolled asthma for participation in subsequent research. Patients were excluded from this research if, in the initial online questionnaire, they indicated that they did not have a diagnosis of asthma, if they had a diagnosis of chronic obstructive pulmonary disease, or if they were current smokers. In addition, eligible patients were to be symptomatic, and were to be receiving therapy with a long-acting β_2 -agonist and an inhaled corticosteroid.

All patients who met the criteria for severe, uncontrolled asthma agreed to take part in the study, and those who provided contact details were then contacted by a call center. Patients who were interested in the research were then referred to a physician

at a participating site, with the sites being distributed throughout Germany to ensure geographical coverage of the study. At the site visit, physicians confirmed the diagnosis of severe, uncontrolled asthma (defined as asthma that remained symptomatic despite Global Initiative for Asthma Step IV medication). No further selection criteria were applied, with the intention that the population recruited was representative of patients with severe, uncontrolled asthma across Germany, and patients were not randomized.

STUDY DATABASES

Two databases were used in this study. (1) The results of the initial online questionnaire were captured in ClinLife Version 3.5 (Clariness AG, Zurich, Switzerland). (2) At the participating sites, physicians recorded patient data in paper case report forms; these were then entered into the project database by a contract research organization, with the data stored on a PostgreSQL database server, with Microsoft Access 2016 used as front end for accessing and processing the data.

RESULTS

TABLE E1. List of allergens for specific IgE testing

General allergen sources	Allergen species (scientific name) Laboratory code [mix]	Patients (%) sensitized (N = 356)	sIgE (kU/L), median (interquartile range)
Perennial allergens			
Mammalian allergens	Cat (<i>Felis domestica</i>) e1	124 (34.8)	4.98 (1.03, 16.55)
	Fel d 1 (<i>Felis domestica</i>) e94	103 (28.9)	4.33 (1.33, 11.6)
	Dog (<i>Canis familiaris</i>) e5	113 (31.7)	3.51 (0.99, 9.72)
	Horse (<i>Equus caballus</i>) e3	76 (21.3)	1.75 (0.92, 7.62)
	Pet epithelium mix ex1 [e1, e3, e4, e5]	128 (36.0)	3.70 (0.99, 9.06)
	Rodent epithelium mix ex70 [e6, e82, e84, e87, e88]	68 (19.1)	1.19 (0.67, 4.33)
Insect allergens	Berlin beetle (<i>Trogoderma angustum</i>) i76	16 (4.5)	0.51 (0.38, 0.84)
	German cockroach (<i>Blattella germanica</i>) i6	42 (11.8)	0.80 (0.58, 1.53)
	Mulberry silk moth (<i>Bombyx mori</i>) i8	67 (18.8)	1.03 (0.58, 2.32)
House dust mites	<i>Dermatophagoides farinae</i> d2	108 (30.3)	2.92 (0.87, 15.85)
	<i>Dermatophagoides pteronyssinus</i> d1	102 (28.7)	3.20 (0.82, 16.80)
	House dust mix hx2 [h2, d1, d2, i6]	139 (39.0)	2.13 (0.85, 11.7)
Storage mites	<i>Acarus siro</i> d70	69 (19.4)	1.44 (0.65, 3.07)
	<i>Blomia tropicalis</i> d201	69 (19.4)	0.98 (0.57, 2.40)
	<i>Euroglyphus maynei</i> d74	67 (18.8)	1.77 (0.69, 5.71)
	<i>Tyrophagus putrescentiae</i> d72	63 (17.7)	1.05 (0.62, 2.47)
Mold/microorganism	<i>Alternaria alternata</i> m6	52 (14.6)	2.85 (1.09, 4.88)
	<i>Aspergillus fumigatus</i> m3	46 (12.9)	0.95 (0.55, 3.58)
	<i>Aspergillus</i> mix mx4 (m3, m36, m207, m228)	30 (8.4)	1.26 (0.59, 3.72)
	<i>Aspergillus niger</i> m207	16 (4.5)	0.83 (0.58, 4.74)
	<i>Aspergillus terreus</i> m36	16 (4.5)	1.32 (0.55, 2.48)
	<i>Candida albicans</i> m5	50 (14.0)	1.27 (0.59, 3.45)
	<i>Cladosporium herbarum</i> m2	25 (7.0)	1.53 (0.50, 6.80)
	Mold mix mx2 [m1, m2, m3, m5, m6, m8]	69 (19.4)	1.73 (0.85, 5.93)
	<i>Mucor racemosus</i> m4	19 (5.3)	1.14 (0.57, 3.51)
	<i>Penicillium chrysogenum</i> m1	33 (9.3)	0.98 (0.59, 3.74)
	<i>Phoma betae</i> m13	34 (9.6)	1.02 (0.67, 2.92)
	<i>Rhizopus nigricans</i> m11	17 (4.8)	1.18 (0.59, 1.60)
	<i>Setomelanomma rostrata</i> m8	32 (9.0)	0.91 (0.59, 2.13)
	<i>Staphylococcus aureus</i> Enterotoxin A m80	22 (6.2)	0.78 (0.52, 1.57)
	<i>Staphylococcus aureus</i> Enterotoxin B m81	36 (10.1)	0.89 (0.46, 1.97)
Seasonal pollen allergens			
Major and cross-reactive minor pollen allergens (pollen species)	Amb a 1 (<i>Ambrosia artemisiifolia</i>) w230	3 (0.8)	0.74 (0.51, 1.44)
	Art v 1 (<i>Artemisia vulgaris</i>) w231	32 (9.0)	1.76 (0.93, 6.56)
	Bet v 1 (<i>Betula verrucosa</i>) t215	124 (34.8)	5.80 (1.71, 20.55)
	Ole e 1 (<i>Olea europaea</i>) t224	25 (7.0)	1.58 (1.12, 3.81)
	*Phl p 7 polcalcin (<i>Phleum pratense</i>) g210	11 (3.1)	3.85 (0.92, 21.30)
	*Phl p 12 profilin (<i>Phleum pratense</i>) g212	10 (2.8)	1.60 (0.78, 2.81)
	Phl p 1 and Phl p 5 (<i>Phleum pratense</i>) g213	139 (39.0)	4.49 (1.61, 19.2)
	Pla l 1 (<i>Plantago lanceolata</i>) w234	8 (2.2)	0.86 (0.40, 3.03)

*Minor allergen.

TABLE E2. Characteristics of individuals included in the analysis

Parameter	Individuals (N = 356)
Sex, male, n (%)	80 (22.5)
Age (y), mean $\pm$ SD	
At diagnosis	28.7 $\pm$ 17.6
On entry to study	46.1 $\pm$ 13.2
Time since diagnosis (y), mean $\pm$ SD	17.6 $\pm$ 14.0
Smoking status, n (%)	
Nonsmoker	155 (43.5)
Current smoker	56 (15.7)
Former smoker	145 (40.7)
Occurrence of allergies, hay fever, asthma, or atopic dermatitis in family, n (%)	227 (63.9)
Current asthma symptoms, n (%)	
Dyspnea	334 (93.8)
Wheezing	244 (68.5)
Cough	300 (84.3)
Chest tightness	257 (72.2)
Other	71 (19.9)
Emergency treatment in the previous 12 mo, n (%)	114 (32.9)
Exacerbations resulting in hospitalization in the previous 12 mo, mean (SD); range	1.8 (2.1); 0-12
Allergic comorbidities, n (%)	281 (78.9)
Rhinitis or rhinoconjunctivitis	218 (61.2)
Food allergy	115 (32.3)
Neurodermatitis	82 (23.0)
Other	58 (16.3)
Type not specified	15 (4.2)
Maintenance asthma medication, n (%) [*]	
ICS plus LABA	200 (56.2)
ICS plus LABA plus LTRA	38 (10.7)
ICS plus LABA plus LAMA	30 (8.4)
ICS plus LABA plus systemic steroid	21 (5.9)
ICS plus LABA plus LAMA plus systemic steroid	15 (4.2)
ICS plus LABA plus LAMA plus LTRA	9 (2.5)
ICS plus LABA plus LTRA plus systemic steroid	9 (2.5)
ICS plus LABA plus LAMA plus LTRA plus systemic steroid	8 (2.2)
ICS plus LABA plus xanthine derivative	5 (1.4)
Other (excluding systemic steroid) [*]	11 (3.1)
Other (including systemic steroid) [*]	10 (2.8)

ICS, Inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.

^{*}"Other" contains fewer than 5 patients per combination.