

Results of drug hypersensitivity evaluations in a large group of children and adults

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Summary

Background Proven IgE or T-cell mediated drug hypersensitivity reactions (DHRs) seem less common in children compared with adults. However, this has never been proved by data.

Objective To determine and compare proven DHR prevalence in children and adults.

Methods Using the DAHD (*Drug Allergy and Hypersensitivity Database*) cohort, children with proven DHRs were compared with adults. The international EAACI-ENDA recommendations were followed. Patients were divided into four groups: index reaction and test during childhood (C/C), index reaction at childhood and test at adulthood (C/A), index reactions at childhood and adulthood and test at adulthood (CA/A), index reaction and test at adulthood (A/A).

Results A total of 3275 patients (67.9% female), comprising a total of 4370 patient-episodes, were evaluated (74.5% belonged to the A/A group). Prevalence of positive tests was 15.2% (95%CI, 14.1–16.2) for all tested classes, 10.6% (8.3–13.0) for C/C, 10.6% (7.5–13.6) for C/A, 22.1% (12.8–31.3) for CA/A and 16.5% (15.2–17.8) for A/A. The prevalence was lower in group C/C compared with groups A/A ($P < 0.0001$) and CA/A ($P = 0.003$). It was also lower in group C/A compared with the two latter groups (respectively $P = 0.003$ and $P = 0.005$). Significant differences were found for maculopapular exanthemas only, and not for urticaria/angioedema and anaphylaxis. The difference was mainly observed with β -lactams and not for NSAIDs.

Conclusion and Clinical Relevance Suspicions of DHRs are less likely to be confirmed in children.

Keywords DAHD database, diagnosis, drug allergy, drug hypersensitivity, risk prediction

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Introduction

Adverse drug reactions (ADRs) are noxious or unintended reactions to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis, or treatment [1]. They are classified into type A (dose dependent and predictable) and type B (not dose dependent and unpredictable) reactions [2]. The latter include drug allergic or non-allergic hypersensitivity reactions (DHRs). A drug allergy is always associated with an immune mechanism for which evidence can be shown of drug-specific antibodies or activated T lymphocytes [3, 4].

ADRs have a huge impact on clinical practice, drug development and public health [3, 5]. A meta-analysis from a hospitalized USA population [6] found a prevalence of ADRs of 15.1% and 6.5% of emergency consultations and 6.1% in hospital admissions in a French study [7]. From these studies, a review [3] concluded that DHRs represent about one-third of ADRs. In paediatric populations, a systematic review and meta-analysis [8] concluded that in hospitalized children, the overall incidence of ADRs was 9.5%, and that for outpatient children, it was 1.5%. A recent large study from the USA found that the overall incidence of self-reported antibiotic allergy was 15.3%, and that increasing age

had a significant correlation to antibiotic allergy prevalence [9]. Nonetheless, these data are based on studies, which in most cases, have addressed ADRs in general, ignoring the underlying mechanism.

Indeed, a study on children in Portugal [10] highlighted the fact that ADRs are frequently reported [10.2%] and that many children are classified as having a drug allergy. However, after a complete evaluation, very few of these reactions can be attributed to DHRs. It is assumed that in children, most of the skin reactions are attributable to infectious diseases or interactions between drugs and infectious agents rather than to the drug itself [11, 12]. Although it is mandatory to appraise drug-allergy epidemiology, the diagnostic work-up for DHRs is complex, time consuming, sometimes dangerous and varies widely from centre to centre [13] despite European efforts to standardize procedures [14–17].

Furthermore, the time elapsed between the reaction and the allergy testing must be considered when negative results emerge, because IgE-mediated hypersensitivity may decline more rapidly than T-cell mediated hypersensitivity in the absence of antigen exposure [15–18].

In the present study, we aimed to determine and compare proven DHR prevalence in children and adults.

Methods

Patient selection

Patients were selected from our *Drug Allergy and Hypersensitivity Database* (DAHD®). This prospective cohort included all the patients who consulted at our allergy clinic (University Hospital of Montpellier, France) between September 1996 and July 2009 with a clinical history suggestive of DHR and who completed the drug-allergy work-up. Patients who had experienced severe life-threatening skin reactions, drug-induced autoimmune diseases or severe organ involvement were excluded due to the fact that drug provocation tests (DPTs) are contraindicated in these cases [16]. Patients also underwent skin tests (STs) to the common aeroallergens of the area. Atopic patients were defined as those having at least one positive skin prick test with the standardized battery of the most common aeroallergens of our region. The local ethics committee approved the present study, the DAHD and the DPT (performed routinely).

Drug-allergy work-up

We based our protocols on European Network for Drug Allergy (ENDA) recommendations [14–16]. After completing the standardized ENDA questionnaire on drug

allergy [14] and signing a written informed consent, patients underwent STs, if available. The test sequence was: (i) Skin prick tests (1/10 concentration for anaphylactic reactions and full strength) at intervals of 15–20 min, (ii) intradermal tests (1/100 for severe anaphylactic reactions, 1/10 and full-strength concentrations) at intervals of 20–30 min. The procedure ended when a positive ST was found, i.e. in the following cases: (i) the weal was larger than 3 mm and accompanied by erythema with a negative response to the control saline after ST; (ii) there was a 3 mm change in the diameter of the initial weal associated with a flare and a negative control reagent after intradermal tests. A late reading test in patients with unknown chronology or with a non-immediate reaction was performed after 24–72 h. When STs were negative or not validated, a DPT with the suspected drug was performed under strict hospital surveillance [19], as recommended [16]. Patients ingested increasing doses of the drug every 30 min until the usual daily dose was administered or until symptoms of a drug reaction occurred. The number of steps and cumulative dose were adapted for children according to their weight. Administration was single-blinded and performed by a physician with full resuscitation back-up. Patients had not taken any antihistamines or drugs the previous week that could have affected STs or DPTs. Patients on β -blockers and with an anaphylactic reaction in their clinical history were asked to visit their cardiologist to stop the drug 2 days before STs and/or DPTs. The DPT was considered positive in cases of objective reaction, compatible with the previous episode(s). In cases of unclear reaction (subjective symptoms such as gastric pain or isolated pruritus) or non-compatible reaction with the previous episode(s), the test was repeated and double-blinded, placebo-controlled.

Classification of the patients

Child was defined as an individual aged 0–18 years of age. The index reaction was defined as the history of DHR associated with drug intake. Some of the patients have had a DHR and have been tested for more than one drug class; therefore, the study focused on tested drug classes (tested classes). A tested class was composed of the index reaction to one drug class and the corresponding drug-allergy work-up. If a patient had an index reaction involving two drugs belonging to two different drug classes, then two tested classes were considered. If a patient had suffered several DHRs to several drugs from the same drug class (i.e. amoxicillin and cefuroxime, both part of the β -lactam family), then only one tested class was considered. In that case, the patient was 'positive' (allergic/hypersensitive) for the drug class, if at least one test was positive and negative

if all the tests were negative. When a patient reported several histories for the same drug class, the last clinical history was considered for the index reaction clinical presentation, assuming that the last reaction was at least as severe as the previous ones.

According to the age at index reaction and the age at drug-allergy testing, the association suspicion/test for each drug class was divided into four groups:

- 1 Group 1 (C/C): Index reaction(s) (C) and test during childhood (C).
- 2 Group 2 (C/A): Index reaction(s) during childhood (C) and test during adulthood (A).
- 3 Group 3 (CA/A): Index reactions during both childhood and adulthood (CA), and test during adulthood (A).
- 4 Group 4 (A/A): Index reaction(s) (A) and test during adulthood (A).

Thus, focusing on tested classes allowed a patient to be classified into different groups depending on the tested classes. For instance, an adult patient with one reaction to β -lactam antibiotics during childhood and two reactions to different NSAIDs in adulthood would appear within the study in two tested classes: the first one with β -lactam in the C/A group, and the second one with NSAIDs in the A/A group. This way, one patient could be included in several different groups. In contrast, a patient with several reactions during childhood and adulthood to β -lactam antibiotics would appear only once as β -lactam tested class and belonging to the CA/A group.

Statistics

Data were expressed either in frequencies and per cent (with 95% CI) or in median (with interquartiles). Comparisons were respectively made using chi-squared tests (or Fisher exact tests) or Wilcoxon Mann–Whitney tests.

To assess the robustness of the results, a sensitivity analysis was conducted in which only one tested class per patient and per group was considered. For patients with more than one tested class per group, a random selection of the tested classes was performed, using

SAS software (a random number was attributed to each drug class, and for a patient with several drug class tested, the one with the lowest random number was selected). Statistics were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA), and the first type error was set at 5%.

Results

Description of the patient groups

A total of 3275 patients were evaluated: 2432 (74.3%) were tested for only one drug class and 843 (24.7%) for more than one drug class, representing a total of 4370 tested classes or 1.3 ± 0.6 tested classes per patient (Table 1). The majority of patients were females (67.9%). For nearly three quarters of the tested classes (3256–74.5%), both index reaction(s) and tests were during adulthood (group A/A). For 658 (15.1%), both index reaction(s) and tests were during childhood (group C/C). Seventy-three patients were represented in two different groups, and three in three different groups. Among the 4370 tested classes, which included 2698 (61.7%) DPTs and 1672 (38.3%) STs, 664 (15.2%, 95%CI [14.1–16.2]) were catalogued as positive, according to ENDA standards, and consequently the diagnosis of DHR (later named 'positive tested classes') was determined.

The rates of positive tested classes were respectively 10.6% [8.3–13.0] for group C/C, 10.6% [7.5–13.6] for group C/A, 22.1% [12.8–31.3] for group CA/A and 16.5% [15.2–17.8] for group A/A. The prevalence was similar between groups C/C and C/A ($P = 0.96$) and groups CA/A and A/A ($P = 0.19$). However, the prevalence was lower in group C/C compared with groups A/A ($P < 0.0001$) and CA/A ($P = 0.003$). Prevalence was also lower in group C/A compared with the two latter groups (respectively $P = 0.003$ and $P = 0.005$).

Risk prediction according to age at suspicion and time delay between the last suspicion and the test

Overall, the median age at the first reaction was 34 years [17–49] and the age at the last reaction was

Table 1. Description and distribution of the groups

Group	Age at suspicion		Age at testing		Tested class N (%)	Number of repetitions per patient within groups				Number of patients
	Child	Adult	Child	Adult		Mean (SD)	1	2	More than 2	
Group 1 (C/C)	X		X		658 (15.1)	1.3 (0.6)	386 (76.0)	99 (19.5)	23 (4.5)	508
Group 2 (C/A)	X			X	379 (8.7)	1.1 (0.4)	298 (88.7)	33 (9.8)	5 (1.5)	336
Group 3 (CA/A)	X	X		X	77 (1.8)	1.0 (0.1)	75 (98.7)	1 (1.3)	0	76
Group 4 (A/A)		X		X	3256 (74.5)	1.3 (0.6)	1805 (74.2)	474 (19.5)	155 (6.4)	2434
Total					4370	1.3 (0.6)	2432 (74.3)	639 (19.4)	200 (6.1)	3275*

*Respectively, 73 and 3 patients are represented in two and three different groups.

35 years [19–50] (Table 2). The age at testing was 42 years [27–56], and the delay between the index reaction and the allergy testing was 1.3 years [0.4–8.9].

The ages at first and last reactions and the delay between the index reaction and the test were similar for the tested classes, with at least one reaction during adulthood (groups CA/A and A/A), regardless of the result of the test. However, for groups C/C and C/A, patients were older at first and last reactions when the result of the test was positive ($P < 0.001$ for group C/C and $P < 0.01$ for group C/A). Concerning the delay between the index reaction and the test, it was the same regardless the result of the tested class for groups C/A and CA/A, but was shorter for groups C/C and A/A.

Risk prediction according to certain co-morbidities

Asthmatics were equally represented regardless of the result of the test (Table 3). However, the proportion of atopics appeared to be slightly higher for positive tested classes in groups C/C and A/A.

Risk prediction according to clinical presentation

Considering the clinical presentations of DHRs, the suspected reactions were mostly urticaria/angioedema/pruritus (1993–45.6%), followed by maculopapular exanthema (798–18.3%), anaphylaxis (702–16.1%), anaphylactic shock (373–8.5%), isolated respiratory symptoms (102–2.3%) and undetermined skin reactions (82–1.9%). The highest positive rate was observed for anaphylactic shock and anaphylaxis (28.7% and 20.7%). The lowest rates were observed for isolated respiratory symptoms (10.8%), maculopapular exanthema (10.8%), undetermined skin reactions (11.0%) and urticaria/angioedema/pruritus (13.3%) (Table 4).

Considering the chronology of the reactions (delay between the drug intake and the beginning of the index reaction), 1192 (27%) were immediate (i.e. occurring less than 1 h after the last drug administration), and 2489 (57%) were non-immediate (i.e. occurring more than 1 h after the last drug administration). However, in 689 (15.8%) reactions, the chronology was unknown. According to the patient group, the reaction occurred

Table 2. Distribution of median (25–75th percentiles) age at suspicion testing and delay between the groups according to the test results

Group	C/C	C/A	CA/A	A/A	Total
Age at first suspicion	6 (3–11)	9 (5–14)	10 (7–15)	41 (30–53)	34 (17–49)
Positive	10 (6–13)	10.5 (7–16)	10 (3–16)	40 (31–52)	35 (21–50)
Negative	6 (3–11)	8 (5–14)	10 (7–15)	41 (30–53)	33 (16–48)
<i>P</i>	<0.001	0.01	0.90	0.44	0.002
Age at index reaction	7 (4–12)	10 (5–14)	27 (21–33)	42 (31–54)	35 (19–50)
Positive	11 (7–13)	12 (7–16)	28 (25–32)	42 (32–54)	38 (24–51)
Negative	6 (3–11)	9 (5–14)	25.5 (21–33.5)	42 (31–54)	34.5 (17–49)
<i>P</i>	<0.001	0.01	0.26	0.59	<0.001
Age at testing	11 (8–14)	28 (23–36)	32 (26–37)	48 (37–59)	42 (27–56)
Positive	12 (9–15)	30 (23.5–39.5)	32 (30–33)	47 (36–58)	42 (30–56)
Negative	10.5 (8–14)	28 (23–36)	32 (23.5–37)	48 (37–60)	42 (26–56)
<i>P</i>	0.01	0.20	0.77	0.07	0.05
Delay*	1.10 (0.39–4.95)	19.26 (13.32–28.04)	1.41 (0.52–6.13)	0.92 (0.34–5.77)	1.29 (0.38–8.88)
Positive	0.4 (0.3–2.5)	18.7 (12–31.1)	1.3 (0.3–5.3)	0.7 (0.3–3.7)	0.8 (0.3–4.9)
Negative	1.4 (0.4–5.6)	19.4 (13.4–28)	1.4 (0.6–6.7)	1 (0.4–6.5)	1.5 (0.4–9.4)
<i>P</i>	<0.001	0.90	0.34	<0.001	<0.001

*Delay in years between the index reaction and the allergy testing.

Table 3. Distribution of positive tests according to co-morbidities

Reaction <i>n</i> (%)	C/C		C/A		CA/A		A/A		Total	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Asthmatic	13 (13.1)	86 (86.9)	6 (10.5)	51 (89.5)	4 (25.7)	11 (73.3)	61 (21.0)	230 (79.0)	84 (18.2)	378 (81.8)
Non-Asthmatic	43 (10.5)	366 (89.5)	27 (9.7)	252 (90.3)	13 (21.3)	48 (78.7)	359 (16.8)	1784 (83.3)	442 (15.3)	2450 (84.7)
<i>P</i>	0.46		0.84		0.73		0.07		0.11	
Atopic	43 (15.4)	236 (84.6)	18 (9.5)	171 (90.5)	13 (30.2)	30 (69.8)	221 (19.3)	924 (80.7)	295 (17.8)	1361 (82.2)
Non-Atopic	13 (5.7)	216 (94.3)	15 (10.2)	132 (89.8)	4 (12.1)	29 (87.9)	199 (15.4)	1090 (84.6)	231 (13.6)	1467 (86.4)
<i>P</i>	<0.001		0.84		0.06		0.01		<0.001	

within the first hour for 22% (group C/C) to 34.6% (group A/A); and after 24 h for 29.8% (group C/A) to 40.6% (group CA/A) (Table 5).

Risk prediction according to the number of reactions

According to the number of reactions (episodes that resemble or recall drug allergy), the rates of positive tests were higher among the subjects with several reactions to the same drug class than those with a single one (22.0% vs. 13.7%, Table 6).

Risk prediction according to the drug class involved

Among the tested classes, the most frequently involved were β -lactam antibiotics, with 1639 (37.5%) index reactions, including 269 positive tests (40.5% of all positive tests and 16.4% of β -lactam index reactions). The NSAIDs accounted for 20.7% of the proven DHRs (151) and 16.6% of the 907 NSAID-tested classes. Whatever the drug class, except for NSAIDs, the rate of positive tests was lower in group C/C than in the other groups, especially for antibiotics and acetaminophen (Table 7).

Sensitivity analysis

The sensitivity analysis focused on 3354 tested classes (508 in group C/C, 336 in group C/A, 76 in group CA/A

and 2434 in group A/A), involving 3275 patients. Seventy-three patients were represented in two different groups, and three in three groups. Similar results were observed (see on-line tables).

Discussion

The present study performed in 3275 patients with a suspicion of DHRs, reports the results of the 4370 tested drug classes. A positive test was found for 664 (15.2%). When the first reaction occurred during childhood, the prevalence rate of positive tested class was similar whether the test was during childhood (10.6%) or adulthood (10.6%); thus, one could argue that drug allergy in childhood does not resolve with time. However, the

Table 6. Distribution of positive tests according to the groups and the number of episodes

Group	C/C	C/A	CA/A	A/A	Total
<i>n</i> (%)	658	379	77	3256	4370
At least one suspicion	70 (10.6)	40 (10.6)	17 (22.1)	537 (16.5)	664 (15.2)
Only one suspicion	50 (9.2)	36 (10.2)	0	403 (15.0)	489 (13.7)
More than one suspicion	20 (17.7)	4 (15.4)	17 (22.1)	134 (23.1)	175 (22.0)

Table 4. Distribution of positive tests according to the type of clinical index reactions

Reaction <i>n</i> (%)	C/C		C/A		CA/A		A/A		Total	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Urticaria/Angioedema/Pruritus	39 (11.0)	316 (89.0)	15 (8.1)	170 (91.9)	5 (19.2)	21 (80.8)	206 (14.4)	1222 (85.6)	265 (13.3)	1729 (86.7)
Maculopapular exanthema	5 (3.1)	157 (96.9)	10 (11.4)	78 (88.7)	3 (17.7)	14 (82.3)	68 (12.8)	463 (87.2)	86 (10.8)	712 (89.2)
Anaphylaxis	17 (22.4)	59 (77.6)	7 (17.5)	33 (82.5)	4 (26.7)	11 (73.3)	117 (20.5)	454 (79.5)	145 (20.7)	557 (79.3)
Anaphylactic shock	7 (31.9)	15 (68.2)	2 (11.8)	15 (88.2)	2 (40.0)	3 (60.0)	96 (29.2)	233 (70.8)	107 (28.7)	266 (71.3)
Respiratory symptoms	1 (14.3)	6 (85.7)	1 (25.0)	3 (75.0)	1 (25.0)	3 (75.0)	8 (9.2)	79 (90.8)	11 (10.8)	91 (89.2)
Undetermined skin reaction	1 (9.1)	10 (90.9)	0 (0)	6 (100)	1 (50.0)	1 (50.0)	7 (11.1)	56 (88.9)	9 (11.0)	73 (89.0)
Others	0 (0)	25 (100)	5 (12.8)	34 (87.2)	1 (12.5)	7 (87.5)	35 (14.2)	212 (85.8)	41 (12.9)	278 (87.1)
Total	70 (10.6)	588 (89.4)	40 (10.6)	339 (89.4)	17 (22.1)	60 (77.9)	537 (16.5)	2719 (83.5)	664 (15.2)	3706 (84.8)

Table 5. Distribution of positive tests according to the chronology of the index reaction

Chronology <i>n</i> (%)	C/C		C/A		CA/A		A/A		Total	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
<1 h	28 (22.0)	99 (78.0)	7 (11.1)	56 (88.9)	5 (27.8)	13 (72.2)	221 (22.5)	763 (77.5)	261 (21.9)	931 (78.1)
1–6 h	14 (11.6)	107 (88.4)	6 (16.2)	31 (83.8)	2 (25)	6 (75)	76 (15.2)	425 (84.8)	98 (14.7)	569 (85.3)
6–24 h	8 (8.4)	87 (91.6)	5 (10.9)	41 (89.1)	3 (25)	9 (75)	65 (15.7)	349 (84.3)	81 (14.3)	486 (85.7)
>24 h	13 (5.8)	211 (94.2)	4 (6.4)	58 (93.6)	4 (15.4)	22 (84.6)	121 (12.8)	822 (87.2)	142 (11.3)	1113 (88.7)
Unknown	7 (7.7)	84 (92.3)	18 (10.5)	153 (89.5)	3 (23.1)	10 (76.9)	54 (13.0)	360 (87.0)	82 (11.9)	607 (88.1)
Total	70 (10.6)	588 (89.4)	40 (10.7)	339 (89.3)	17 (22.1)	60 (77.9)	534 (16.5)	2719 (83.5)	664 (15.2)	3706 (84.8)

Table 7. Distribution of positive tests according to the suspected drug class

Group/drug <i>n</i> (%)	C/C		C/A		CA/A		A/A		Total	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
β-lactams	31 (9.6)	292 (90.4)	22 (9.2)	218 (90.8)	9 (18.4)	40 (81.6)	207 (20.2)	820 (79.9)	269 (16.4)	1370 (83.6)
NSAIDs	29 (18.5)	128 (81.5)	10 (16.7)	50 (83.3)	7 (31.8)	15 (68.2)	105 (15.7)	563 (84.3)	151 (16.7)	756 (83.3)
Other antibiotics	5 (7.8)	59 (92.2)	2 (8.3)	22 (91.7)	1 (33.3)	2 (66.7)	97 (24.7)	296 (75.3)	105 (21.7)	379 (78.3)
Radiocontrast media	0 (0)	3 (100)	4 (66.7)	2 (33.3)	0	0	26 (12)	190 (88)	30 (13.3)	195 (86.7)
Paracetamol	2 (5.6)	34 (94.4)	2 (14.3)	12 (85.7)	0 (0)	1 (100)	25 (12.6)	174 (87.4)	29 (11.6)	221 (88.4)
Corticosteroids	0 (0)	5 (100)	0 (0)	4 (100)	0	0	6 (8.2)	67 (91.8)	6 (7.3)	76 (92.7)
Local anaesthetics	0 (0)	30 (100)	0 (0)	23 (100)	0 (0)	2 (100)	6 (2.7)	217 (97.3)	6 (2.2)	272 (97.8)
Opiates	0 (0)	3 (100)	0 (0)	2 (100)	0	0	1 (1.7)	57 (98.3)	1 (1.6)	62 (98.4)
Others	3 (8.1)	34 (91.9)	0 (0)	6 (100)	0	0	64 (16.0)	335 (84.0)	67 (15.2)	375 (84.8)
Total	70 (10.6)	588 (89.4)	40 (10.6)	339 (89.4)	17 (22.1)	60 (77.9)	537 (16.5)	2719 (83.5)	664 (15.2)	3706 (84.8)

rate of positive tested classes was higher when the index reaction and the resulting tests occurred during adulthood (16.5–22.1%). Finally, the rate of positive tested classes was higher when several reactions to the same drug class were observed (22%).

In 2004, we published [19] the results of 1372 DPTs on patients with a suggestive history of DHRs and found a positivity rate of 17.4%. However, the database was not strong enough at that time to address the particular question of the present article. Our current sample includes the before-mentioned studies and is much larger (4370 tested classes). In an Austrian study, Wöhrle *et al.* [20] performed the drug-allergy work-up and were able to confirm drug responsibility in 100 of 325 cases, i.e. with a higher positivity rate of 30.8%. In children, Rebelo-Gomes *et al.* [10] found a lower prevalence (8.7%) in 34 suspected DHRs. Therefore, positivity rate may vary from centre to centre, possibly due to selection biases; indeed, maybe more severe cases are referred to one centre compared with another.

The present study was based on tested classes and not on patients. The choice to use tested classes was preferred for several reasons. First, we wanted to answer the question of whether or not children are at lower risk of true drug hypersensitivities compared with adults. Secondly, we made the choice not to focus on a specific drug class, but to include all the drug classes in the study. By consequence, it was not possible to identify other risk factors at the patient level.

One could argue that our main finding was based on a selection bias, as some patients were included several times. The impact of such repetition is however low. First, the proportion of patients with several tested classes in the same group was limited, only 843 of 3275 (25.7%). That proportion was similar in groups C/C and A/A (respectively 24.0% and 25.8%). Secondly, in most cases, repetitions comprised several suspicions involv-

ing different drug classes. Finally, the sensitivity analysis reported similar results. The consistency of the results reinforced the fact that the bias induced by repetition is limited.

One could argue that the differences observed could be due to differences in the diagnostic procedures. However, this impact is reduced as the drug-allergy work-up is standardized, does not depend on the age of the patient, and follows the ENDA international recommendations [14–17]. Moreover, drug-allergy work-ups for children and adults were performed in the same centre, reducing a potential centre effect.

Differences between prevalences in children and adults can be partially explained by the fact that children have had less contact with drugs, and the pattern of drug hypersensitivity follows the prescription patterns. In children, exanthems during antibiotic courses can be difficult to assess [12, 21]. Maculopapular eruptions that are not pruritic occur frequently, as has been observed in 3–7% of children taking ampicillin in one study [22]. They emerge during antibiotic treatment and rarely after. These exanthems are very unlikely to be allergic and their mechanisms are not well studied. Furthermore, the immune response that a patient develops for a viral infection can alter the immune response to an antibiotic, resulting in an allergic-like reaction specifically to that antibiotic, which is highly unlikely to recur [12, 21].

Due to the variety of clinical manifestations of drug hypersensitivity [3, 23], we concentrated on common reactions. We found a similar rate of proven DHRs in C/C and A/A groups when anaphylaxis, anaphylactic shock, urticaria/angioedema/pruritus were the suspected clinical manifestations (comprising 20%, 30% and 10% of the cases respectively). When of allergic nature, these reactions are usually related to IgE-mediated mechanisms. In maculopapular exanthemas, however, reactions are associated with T-cell mechanisms, a remarkable difference of proven reactions was found

between C/C and A/A (3.1% vs. 12.8%). This reinforces the fact that maculopapular exanthemas in children are not usually due to drugs and should clearly be differentiated from urticaria.

Regarding the chronology of the reactions, there were no major differences between the C/C and A/A groups. The highest percentage of positive tests was found when the index reaction happened within the first hour after the last drug administration. These reactions have a higher probability to be IgE-mediated [21].

To conclude, DHR suspicions in adults are 1.5 times more likely to be confirmed than in children, as we were able to demonstrate a higher positivity rate with standardized tests. Overall, important clinical factors in positive tested classes are older age at suspicion, and shorter delay between clinical manifestations and testing. Regarding the clinical manifestations, the proven DHR rate was lower in children presenting with maculopapular exanthems, whereas similar positive tests between children and adults were found among other manifestations. Although actual studies of proven reactions are scarce, further studies are needed to address the real DHR prevalence

among different age populations and also to establish risk factors.

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