ORIGINAL ARTICLE DRUG ALLERGY

Diagnosing multiple drug hypersensitivity in children

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Background: Multiple drug hypersensitivity (MDH) has been defined as a hypersensitivity to two or more chemically different drugs. Two types of MDH have been reported: the first one, which develops to different drugs administered simultaneously and the second type, in which sensitizations develop sequentially. In children, studies which diagnose MDH on the basis of positive allergologic tests to 2 or more chemically different drugs are lacking.

Methods: We conducted a prospective study evaluating children with histories of MDH by skin tests, patch tests, serum-specific IgE assays, and drug provocation tests.

Results: A MDH was diagnosed in 7 (2.5%) of the 279 children evaluated who completed the study. The responsible drugs were β-lactams (penicillins and cephalosporins) in 5 episodes, ibuprofen and anticonvulsants in 3, and erythromycin, fentanyl, methylprednisolone, and cotrimoxazole in 1. Sensitivity to 2 chemically different drugs was diagnosed in 6 children and to 3 drugs in 1 child. Two of the 7 children presented the first type of MDH, whereas 5 displayed the second one.

Conclusions: MDH can occur in children, even to drugs other than antibiotics. It is crucial to evaluate children with histories of MDH using both *in vivo* and *in vitro* allergologic tests, including challenges. In fact, such approach allows the physician to confirm the diagnosis of MDH in a small percentage of children with histories of MDH, as well as to rule it out in the great majority of them.

The revised nomenclature for allergy distinguishes between allergic and non-allergic hypersensitivity reactions to drugs and classifies the former as IgE-mediated or non-IgE-mediated (1). It is important, however, to distinguish between immediate and non-immediate reactions in establishing the diagnosis and management of drug hypersensitivity reactions (2–4). Immediate allergic reactions occur within the first hour after the last drug administration and are manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock. They are thought to be IgE-mediated and are assessed by immediate-reading skin tests, serum-specific IgE assays, and flow cytometric basophil activation tests. Non-immediate reactions occur more than 1 h after the last drug administration. The main non-immediate reactions are maculopapular rash and delayed-appearing urticarial rash. A T-cell-mediated pathogenic mechanism is often involved in maculopapular rashes and other non-immediate reactions such as bullous exanthems and drug-induced hypersensitivity syndrome (5). These reactions can be assessed by delayed-reading skin tests and patch tests, as well as by lymphocyte transformation tests (LTT) and flow cytometric lymphocyte activation tests (2, 5). In evaluating allergic hypersensitivity reactions to drugs, the sensitivity of allergologic tests is not 100%; in selected cases, therefore, provocation tests are necessary.

In non-allergic hypersensitivity reactions to drugs, inflammatory mediators are released by non-specific immunologic mechanisms. The drugs most frequently responsible for such reactions are non-steroidal anti-inflammatory drugs (NSAIDs). In the diagnosis of non-allergic hypersensitivity reactions, skin tests and *in vitro* tests are negative; thus, provocation tests with the suspected drug are essential (2).

Multiple drug hypersensitivity (MDH) has been defined as a hypersensitivity to two or more chemically different drugs (6). Two types of MDH have been reported: one, which develops to different drugs administered simultaneously and another type, in which sensitizations develop sequentially, sometimes years apart (7).

Clinical presentations of MDH include both immediate and non-immediate reactions. The main responsible drugs are

antibiotics, NSAIDs, anticonvulsants, and local anesthetics (7–18).

With regard to the pathogenic mechanisms of MDH, in some studies concerning adults (7, 11, 14, 17), a T-cell-mediated pathogenic mechanism was demonstrated on the basis of positive responses to patch tests, delayed-reading intradermal tests, and/or *in vitro* tests, such as the lymphocyte transformation test and drug-induced IFNγ release. In this connection, Pichler et al. (19) hypothesized that the immune stimulation during the first drug hypersensitivity reaction, like that of viral infections, may lower the threshold of T-cell reactivity to drugs and facilitate the immune response to the second drug. In effect, Daubner et al. (17) recently demonstrated that in MDH patients the drug reactive T cells display an enhanced state of activation; therefore, they may present a lower threshold for activation by drugs.

On the other hand, the positive responses to the autologous serum skin test (ASST) and/or autologous plasma skin test (APST) observed in other studies concerning adults with MDH (13, 15) indicate an autoreactivity, which does not seem to be caused by functional circulating autoantibodies directed against IgE or FcεRI.

Overall, there are only three studies that have described MDH in children (8, 10, 16) and two of them regard only hypersensitivity reactions to antibiotics (8, 10). In the study by Park et al. (10), the diagnosis of multiple antibiotic hypersensitivity was based only on the history; in effect, children did not undergo allergologic tests. In the study by Kamada et al. (8), concerning 120 children with multiple antibiotic hypersensitivity, only 98 of the 115 subjects with histories of hypersensitivity reactions to β-lactams underwent allergologic tests, and 31 displayed positive results. Buonomo et al. (16) studied 278 children with histories of hypersensitivity reactions to drugs, diagnosing a hypersensitivity in 6 (2.2%); 64 (23.5%) of the 272 children with negative results in the allergologic work-up had histories of adverse reactions to almost three drugs. In the latter two studies (8, 16), however, subjects with negative results in allergologic tests did not undergo challenges with the suspected drugs. Therefore, studies which diagnose MDH in children on the basis of positive allergologic tests to two or more chemically different drugs are lacking.

The purpose of our study was to confirm or rule out the diagnosis of MDH in children with histories of hypersensitivity reactions to two or more drugs by evaluating them according to the guidelines of the European Network for Drug Allergy (ENDA), the European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity.

Methods

Patient selection

Children ranging in age from 2 to 14 years were recruited prospectively from a large outpatient population with histories of hypersensitivity reactions to drugs. This population was evaluated between January 2005 and December 2010 in the University Children's Hospital of Belgrade. The inclusion criterion required a history of MDH. The exclusion criteria consisted in severely compromised cardiovascular, renal, or respiratory functions. Prior to the study, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them.

Prick and intradermal skin tests

Children with histories of either immediate or non-immediate reactions to β-lactams were evaluated according to the ENDA guidelines (20, 21).

Prick and intradermal tests were carried out using penicilloyl-polylysine (DAP®; Diater, Madrid, Spain), minor determinant mixture (DAP®; benzyl-penicillin, sodium benzylpenicilloate, and benzyl-penicilloic acid), benzyl-penicillin (Sanavita Pharmaceuticals GmbH, Werne, Germany), and amoxicillin (Bactox; Innothera Group, Chouzy, France). The final concentrations were, respectively, 1.07×10^{-2} mM, 1.5 mM, 10,000 IU/ml, and 20 mg/ml. Benzyl-penicillin and amoxicillin were diluted in normal saline. Phenoxymethylpenicillin was tested at concentrations up to 10,000 IU/ml, any other suspected penicillins were tested at concentrations of 1 and 20 mg/ml, and cephalosporins were used at concentrations up to 2 mg/ml in normal saline.

Children with histories of hypersensitivity reactions to drugs other than β-lactams were evaluated according to the ENDA guidelines (22). The concentrations used were those indicated by such guidelines or, when not specified by them, those available in the literature. Specifically, azythromycin, erythromycin, and cotrimoxazole were tested at concentrations up to 100, 50, and 80 mg/ml, respectively, which are the non-irritating concentrations identified by Empedrad et al. (23). We were unable to test each of the components of cotrimoxazole (trimethoprim and sulfamethoxazole) separately because they were not available in Serbia. Clarithromycin, lidocaine, fentanyl, and methylprednisolone were tested at concentrations up to 0.5 mg/ml, 2 mg/ml, 0.5 μg/ml, and 0.2 mg/ml, respectively. These concentrations proved to be non-irritating in a control group of 30 patients. For injectable drugs, we used the intravenous form, while for non-injectable ones we prepared a solution, as previously described (24).

All reagents – freshly prepared every day under sterile conditions – were initially tested on volar forearm skin by the prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 min later. When prick tests were negative, 0.02 ml of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 min after injections. Results were considered positive when the maximum diameter of the wheal produced by the injection increased by 3 mm or more, accompanied by erythema (4, 22). Positive controls for prick and intradermal tests were performed with histamine (at 10 and 1 mg/ml, respectively). As a negative control for prick and intradermal tests, normal saline was used.

Readings of late reactions to intradermal tests were performed after 48 and 72 h; any infiltrated erythema with a diameter larger than 5 mm was considered a positive reaction. For NSAIDs, skin tests were not performed.

Patch tests

In patients with non-immediate reactions to β-lactams, patch tests were administered with benzyl-penicillin, ampicillin, amoxicillin, and any other suspect β-lactams (5% in petrolatum), in addition to prick and intradermal tests with penicillin reagents, as previously described (21).

In patients with non-immediate reactions to anticonvulsants, patch tests were administered with the suspected drugs – carbamazepine (Hemofarm A.D., Vrsac, Serbia), phenobarbital (Hemofarm A.D.), or lamotrigine (Pharmaswiss, Beograd, Serbia) – at a concentration of 5% in petrolatum. Reagents were prepared by our pharmacy department using the commercially available pure powder.

Children with histories of hypersensitivity reactions to drugs other than β-lactams and anticonvulsants were evaluated according to the ENDA guidelines (22). The concentrations used were those indicated by such guidelines (22) or, when not specified by them, those available in the literature (25). Povidone-iodine was tested at a concentration of 5% in petrolatum.

All reagents were applied to uninvolved skin on the interscapular region of the patient's back, using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, Germany). Occlusion time was 48 h. Readings were made, as recommended by Brockow et al. (22), 15 min after removal of the strips and 24 h later. For NSAIDs, patch tests were not performed.

In vitro tests

Assays (ImmunoCAP System; Phadia, Uppsala, Sweden) were performed, according to the manufacturer's instructions, for specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl. A positive result (i.e., detectable specific IgE antibodies) was defined as a value ≥ 0.35 kU/l. Blood samples were obtained when children were evaluated, and sera were kept at minus 20°C until assayed.

Drug provocation tests (Challenges)

According to the indications and contraindications of the ENDA position paper (26), controlled administrations of therapeutic doses of suspected drugs were also performed in children who displayed negative results in allergologic tests. In those who had experienced immediate reactions, we administered an initial dose of one-hundredth of the therapeutic one (which depended on the children's weight). In cases with negative results, 1 h later we administered a dose of one-tenth and, if the result was again negative, after another hour a full dose. In children with non-immediate reactions, the interval between each dose ranged from 3 days to 1 week (21, 27).

Results

Of the 928 children assessed because of histories of hypersensitivity reactions to drugs, 292 (32.1%) had histories of MDH; however, only 279 completed the study (Table 1). None of the children met the exclusion criteria.

In these 279 children, antibiotics were the most commonly implicated drugs and accounted for 419 reactions in 267 subjects. Among the latter children, 245 had histories of hypersensitivity reactions to β-lactams (168 to penicillins, 70 to

Table 1 Clinical characteristics of the 279 children with histories of multiple drug hypersensitivity (MDH), reported reactions (n. = 606), and suspected drugs

		All patients (n. 279)
Age (years), mean (SD); range (years)		8.7 (3.79); 2 to 14
Girls, n. (%)		125 (44.8)
Time since last drug reaction*, median (range) [25th, 75th percentile]		5 (1–132) [2, 11]
		Reactions, n. (%)
Suspected drugs		
β-Lactams	Amoxicillin	93 [33 plus clavulanic acid] (15.3)
	Benzyl-penicillin	61 (10)
	Phenoxymethyl-penicillin	12 (2)
	Ampicillin	9 (1.5)
	Cephalexin	38 (6.3)
	Ceftriaxone	21 (3.5)
	Cefprozil	18 (3)
NSAIDs	Ibuprofen	88 (14.5)
	Paracetamol	51 (8.4)
	Naproxen	6 (1)
Macrolides	Azythromicin	60 (10)
	Erythromycin	33 (5.4)
	Clarithromycin	22 (3.6)
Sulfonamides	Cotrimoxazole	39 (6.4)
Local anesthetic	Lidocaine	22 (3.6)
Anticonvulsants	Lamotrigine	9 (1.5)
	Carbamazepine	5 (0.8)
	Phenobarbital	2 (0.3)
Aminoglycosides	Gentamicin	8 (1.3)
	Tobramycin	5 (0.8)
Other drugs	Povidone-iodine	2 (0.3)
	Fentanyl	1 (0.1)
	Methylprednisolone	1 (0.1)
Manifestations		
Immediate	Urticaria	37 (6.1)
	Angioedema	28 (4.6)
	Urticaria-angioedema	12 (2)
	Anaphylaxis	3 (0.5)
Non-immediate	Urticaria	280 (46.2)
	Maculopapular rash	172 (28.4)
	Urticaria-angioedema	54 (8.9)
	Angioedema	14 (2.3)
	Fixed drug eruption	4 (0.6)
	Stevens-Johnson syndrome	2 (0.3)

*Time interval (months) between the last drug reaction and the allergologic evaluation.

cephalosporins, and 7 to both) and 167 to non-β-lactam antibiotics. The next group of drugs accounting for hypersensitivity reactions was NSAIDs.

One hundred and seven children had histories of hypersensitivity reactions only to two or more classes of antibiotics, 129 to both antibiotics and NSAIDs and 43 to other combinations.

Thirty-three children had experienced immediate reactions, 180 non-immediate ones and 66 both types of reactions in separate episodes. The most frequent manifestations were delayed-appearing urticaria and maculopapular rash (Table 1).

A hypersensitivity to a single drug was diagnosed in 69 children (24.7%) (Table 2), while a MDH was diagnosed in 7 (2.5%) of the 279 children (Tables 3 and 4); the remaining 203 subjects (72.8%) had negative results in allergologic workups, including drug provocation tests.

With regard to the 69 children sensitive to a single drug (Table 2), all the nine subjects with an IgE-mediated hypersensitivity to benzyl-penicillin had reacted to it; four of these nine subjects displayed skin tests also positive to other penicillin reagents, including amoxicillin, while the two subjects with an IgE-mediated hypersensitivity to amoxicillin were skin test-positive only to it. Moreover, all the 27 children sensitive to NSAIDs had experienced only one reaction to a single compound. In the allergologic workup, those sensitive to ibuprofen or naproxen underwent challenges with paracetamol and tolerated them, while the three children sensitive to paracetamol tolerated ibuprofen challenges. Therefore, all NSAID-sensitive subjects apparently were selective responders.

Of the seven MDH children, two presented a MDH to different drugs administered simultaneously (Table 3), while five had a MDH to different drugs administered sequentially (Table 4). The responsible drugs and clinical manifestations are shown in Tables 3 and 4.

A T-cell-mediated hypersensitivity was diagnosed in five children on the basis of positive responses to patch tests with the responsible drugs (Table 3, patients 1 and 2; Table 4, patients 2, 4, and 5). Two subjects were positive to immediate-reading intradermal tests (Table 4, patients 1 and 4).

Five children (Table 3, patients 1 and 2; Table 4, patients 2, 3, and 5) presented negative results in allergologic tests (when performed), but were positive to drug provocation tests. The reactions observed after such tests were similar or identical to those reported in the history.

Discussion

In this study, the rate of children evaluated because of histories of MDH (30%, 279 of 928 children with histories of hypersensitivity reactions to drugs) falls within the range of 11.4% (97 of 850 subjects) (10) to 40% (120 of 300 children) (8) found in the aforementioned studies concerning MDH in children (8, 10, 16).

In the present study, as in those concerning adults with MDH, the main responsible drugs were antibiotics and NSAIDs, and the most frequent reactions were maculopapular and urticarial eruptions.

Our results, as well as those of other studies concerning adults (7, 11, 14, 17), demonstrate that a T-cell-mediated pathogenic mechanism plays an important role in MDH. In the present study, five of the seven MDH children were positive to

Table 2 Results of the allergologic work-up in the 69 children sensitive to a single drug

	Immediate reactions		Non-immediate reactions				
Culprit drugs	ST +	DPT +	ST* +	ST*-PT +	PT +	DPT +	Total +
β-Lactams							
Benzyl-penicillin	9†	–	–	1	–	–	10
Amoxicillin	2‡	1	1	3	–	3	10
Ampicillin	–	–	–	2	–	–	2
Cefprozil	1	–	–	–	–	2	3
Ceftriaxone	1	–	–	–	–	1	2
Total β-lactams, n.	13	1	1	6	–	6	27
Other drugs							
Ibuprofen	–	12	np	np	np	6	18
Naproxen	–	5	np	np	np	1	6
Cotrimoxazole	1	–	–	–	3	1	5
Lamotrigine	–	–	np	–	2	3	5
Paracetamol	–	2	np	np	np	1	3
Gentamicin	1	–	–	–	1	1	3
Clarithromycin	–	1	–	–	–	1	2
Total positive drugs, n.	15	21	1	6	6	20	69

ST, skin test; DPT, drug provocation test.

*ST delayed-reading intradermal test; PT, patch test; np, not performed.

†Two of them were also positive to penicilloyl-polylysine, minor determinant mixture, and amoxicillin, as well as to ImmunoCAP, 1 was also positive to minor determinant mixture and amoxicillin, and another also to amoxicillin.

‡One of them was positive to ImmunoCAP.

Table 3 Children with MDH to different drugs given simultaneously

Patient/Gender	Age (years)	Clinical manifestations	Time	Responsible drugs	Patch tests	Intradermal tests	DPTs
1/M	10	Delayed-appearing urticaria-angioedema	3 h	Erythromycin	neg	neg	Urticaria/12 h
			3 h	Ibuprofen	np	np	Urticaria-angioedema/2 h
		Maculopapular rash	5 h	Lamotrigine	pos	np	np
2/F	6	Maculopapular rash	6 h	Cephalexin	neg	neg	Maculopapular rash/24 h
		Maculopapular rash	6 h	Phenobarbital	pos	np	np

DPTs, drug provocation tests; np, not performed. Time: the time interval between drug administration and onset of reaction.

Table 4 Children with MDH to different drugs given sequentially

Patient/Gender	Age (years)	Clinical manifestations	Time	Responsible drugs	Time interval	Patch tests	Skin tests	DPTs
1/M	10	Anaphylaxis	10 min	Fentanyl	2 month	np	pos	np
		Anaphylaxis	5 min	Methylprednisolone		np	pos	np
2/F	10	Delayed-appearing urticaria	4 h	Benzyl-penicillin		neg	neg	Urticaria/2 h
		Fixed drug eruption	12 h	Cotrimoxazole	2 year	pos	np	np
3/F	13	Maculopapular rash	10 h	Cephalexin	1 year	neg	neg	Maculopapular rash/6 h
		Angioedema	15 min	Ibuprofen		np	np	Angioedema/10 min
4/M	6	Maculopapular rash	4 h	Phenobarbital	2 year	pos	np	np
		Urticaria	30 min	Amoxicillin		np	pos	np
5/F	9	Stevens-Johnson syndrome	10 h	Ceftriaxone	2 year	pos	np	np
		Delayed-appearing urticaria	3 h	Ibuprofen		np	np	Urticaria/24 h

DPTs, drug provocation tests; np, not performed. Time: time interval between the last drug administration and the onset of reaction; Time interval: time interval between hypersensitivity reactions to different drugs.

patch tests with the responsible drugs; however, none of these five children displayed a T-cell-mediated hypersensitivity to more than one culprit drug.

On the other hand, both this study and literature data suggest that an IgE-mediated pathogenic mechanism is less frequently involved in subjects with MDH. Specifically, only two of our seven MDH children displayed positive responses to immediate-reading intradermal tests, one to both fentanyl and methylprednisolone and the other to amoxicillin.

Overall, two of the seven MDH children had suffered allergic hypersensitivity reactions to all the responsible drugs: one subject had experienced IgE-mediated reactions to both fentanyl and methylprednisolone (Table 4, patient 1) and the other a T-cell-mediated reaction to phenobarbital and an IgE-mediated one to amoxicillin (Table 4, patient 4). With regard to the remaining 5 MDH children, in one, hypersensitivity to both cephalexin and ibuprofen was diagnosed on the basis of positive responses to challenges (Table 4, patient 3); in the other 4 subjects (Table 3, patients 1 and 2; Table 4, patients 2 and 5), an allergic hypersensitivity, either IgE-mediated or T-cell-mediated, to at least one of the responsible compounds (lamotrigine, phenobarbital, cotrimoxazole, or ceftriaxone) was diagnosed on the basis of positive results in allergologic tests, while a hypersensitivity to the other responsible drugs (erythromycin, ibuprofen, cephalexin, and benzyl-penicillin) was diagnosed on the basis of positive responses to drug provocation tests, which, in case of culprit drugs other than ibuprofen, were performed after negative results in allergologic tests. As far as the pathogenic mechanisms of hypersensitivity reactions diagnosed by provocation tests are concerned, those to ibuprofen were likely non-allergic, even though, as with the other NSAIDs, we did not perform allergologic tests with it. However, we cannot exclude an allergic pathogenic mechanism in hypersensitivity reactions to the other responsible drugs, such as antibiotics, even though allergologic tests were negative, particularly if these reactions were not caused by the parent compound but by its metabolites. In such cases, the identification and use of the latter in diagnostic tests are crucial for the diagnosis, as demonstrated by Castrejon et al. (28) with lymphocyte proliferation studies in subjects with hypersensitivity reactions to sulfonamides. Moreover, the fact that patients may have experienced a non-immediate hypersensitivity reaction to an antibiotic – confirmed by a provocation test – but present negative allergologic tests to it might be due to the absence of a concomitant viral infection. In effect, such infections may lower the threshold of T-cell reactivity to drugs (19) or induce polyclonal activation of lymphocytes, as well as maturation of dendritic cells and alterations of drug metabolism (5, 29). With regard to autoreactivity, we did not assess it by

performing ASSTs. In any case, none of the 7 MDH children suffered from chronic urticaria.

It is interesting to note that only one of the 7 MDH children was sensitive to 2 different antibiotics (Table 4, patient 2). Therefore, multiple antibiotic hypersensitivity does not appear to be as frequent as reported by previous studies concerning children (8, 10, 16), in which such diagnosis was based exclusively or mainly on the history. This is not surprising, because both non-immediate maculopapular and urticarial eruptions during antibiotic therapy for an acute febrile illness may be a direct effect of infectious agents, especially viruses (30, 31). Moreover, some non-immediate cutaneous drug reactions during viral infections may also be due to the fact that such infections can concur in causing non-immediate drug hypersensitivity reactions, as previously noted (5, 29). On the other hand, to our knowledge, there are no data indicating that viral infections play a role in IgE-mediated reactions to drugs.

Reactions are referred to as antibiotic allergy when immunologic mechanisms, either IgE-mediated or T-cell-mediated, can be demonstrated. However, literature data indicate that the great majority of children with histories of hypersensitivity reactions to antibiotics, such as β-lactams and macrolides, present negative results in allergologic tests and tolerate challenges with the suspected drugs (31–34). Therefore, drug provocation tests are essential for confirming or excluding an antibiotic hypersensitivity, as recently demonstrated by Caubet et al. (31) in 88 children who had experienced benign skin rashes during penicillin therapy.

Provocation tests with the suspected compounds are also considered the gold standard for establishing or excluding a diagnosis of NSAID hypersensitivity (2, 26, 35). In effect, literature data indicate that the clinical history is not a reliable tool for diagnosing such hypersensitivity, including in children (27, 36). However, a recent study by Doña et al. (37) demonstrated that the clinical history is reliable in subjects who experienced at least two reactions to two or more different NSAIDs.

In the present study, the importance of provocation tests is highlighted by the fact that they allowed us to identify 40 (58%) of the 69 children found sensitive to a single drug, as well as to diagnose seven instances of drug hypersensitivity (3 to ibuprofen, 2 to cephalexin, 1 to erythromycin, and 1 to benzyl-penicillin) in five of the seven MDH children.

With regard to 69 children sensitive to a single drug (Table 2), unlike what was observed in recent studies concerning immediate reactions to penicillins (38), subjects who were skin test-positive to benzyl-penicillin outnumbered those positive to amoxicillin. This phenomenon can be explained by the fact that benzyl-penicillin is still widely used in Serbia; in effect, all the nine subjects with an IgE-mediated hypersensitivity to benzyl-penicillin had reacted to it. As far as the 27 NSAID-sensitive children classified as single reactors are concerned, we must consider that the 24 subjects sensitive to ibuprofen or naproxen did not undergo challenges with alternative strong inhibitors of cyclooxigenase-1, which could have allowed us to identify some cross-reactors.

In conclusion, our study demonstrates that MDH can occur in children, even to drugs other than antibiotics; therefore, it supports the concept that some subjects are likely to develop hypersensitivity reactions to two or more structurally unrelated drugs. This implies that some individuals with a previous hypersensitivity drug reaction may be at higher risk of further reactions to other drugs and should be carefully supervised if they receive potentially sensitizing compounds. However, considering that the history is not a reliable diagnostic tool in children with hypersensitivity reactions to drugs, especially non-immediate ones, it is crucial to evaluate those with histories of MDH using both *in vivo* and *in vitro* allergologic tests, including challenges. In fact, such approach allows the physician to confirm the diagnosis of MDH in a very small percentage of these children, as well as to rule it out in the great majority of them. In particular, by challenging all children with mild reactions and negative results in allergologic tests, we will avoid denying future use of effective drugs to a large number of subjects who would otherwise be falsely labeled "allergic to multiple drugs".

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