

Original Article

Multiple Drug Hypersensitivity Syndrome in a Large Database

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What is already known about this topic? Multiple drug hypersensitivity syndrome is defined as confirmed drug hypersensitivity to at least 2 chemically and pharmacologically unrelated drugs. It is a very rare condition often overestimated because of lack of proper allergy testing.

What does this article add to our knowledge? On the basis of our experience in drug allergy practice, we confirmed that the prevalence of multiple drug hypersensitivity syndrome is very low (0.5%). Among patients with confirmed drug hypersensitivity, the prevalence is 2.5%.

How does this study impact current management guidelines? Further studies should associate *in vivo* and *in vitro* testing to better characterize these patients.

BACKGROUND: Multiple drug hypersensitivity syndrome (MDHS) is defined as confirmed drug hypersensitivity (DH) to at least 2 chemically and pharmacologically unrelated drugs. Reports of MDHS are scarce and poorly specified, and studies that diagnose MDHS on the basis of positive allergy test results are lacking.

OBJECTIVE: To evaluate retrospectively the frequency and characteristics of patients with MDHS in a large database.

METHODS: We included all patients who consulted and were tested in our Allergy Unit between September 1996 and February 2018 for a suspicion of DH. Clinical history and allergy workup results compiled in our *Drug Allergy and Hypersensitivity Database* were reviewed, and data of patients with a diagnosis of MDHS were retrieved and analyzed.

RESULTS: During this period a total of 9250 patients were explored and 1819 tested positive for at least 1 drug. Forty-five cases, 30 female and 15 male patients cumulating 92 DHs, were confirmed as having MDHS. An immunologic mechanism, as demonstrated by positive skin testing, accounted for 59 DHs.

Drug provocation tests were performed to confirm the diagnosis for the remaining 33 DHs. Of the 92 DHs in this series, 38 were classified as type IV and 21 as type I allergies; 33 remained of undetermined mechanism. Drug class occurrences seem to differ from those in monoallergic patients.

CONCLUSIONS: Our data support the concept of MDHS as a distinct and rare subgroup of DH. The prevalence in our database was 2.5% in the total DH alleged patient population and 0.5% of the demonstrated DHs. Skin testing and drug provocation tests are mandatory for confirming the diagnosis. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Multiple drug hypersensitivity; Drug hypersensitivity; Antibiotics; Drug provocation tests; Skin tests

INTRODUCTION

Multiple drug hypersensitivity syndrome (MDHS) was first described in 1989 in an abstract by Sullivan et al¹ as drug allergies to 2 or more chemically different drugs. MDHS is a distinct clinical entity,^{2,3} different from cross-reactivity (due to structural similarities, common metabolic pathways, or pharmacologic mechanisms), flare-up reactions (exacerbation of an existing drug hypersensitivity reaction [DHR] by the early switch of therapy to a novel drug),⁴ or multiple drug intolerance syndrome,^{5,6} which is characterized by adverse reactions to several classes of chemically unrelated drugs without proven immunologic mechanism.

Several authors have addressed the issue of MDHS,⁷⁻¹² with respect to either mechanism⁹⁻¹¹ or frequency.¹² However, reports of MDHS are scarce and mostly based on positive clinical history alone. Hence, self-reported MDHS, rather than documented MDHS, was assessed in antibiotic¹³⁻¹⁵ and nonsteroidal anti-inflammatory drug-allergic^{16,17} patients or in specific populations,¹⁸⁻²⁰ including HIV positive patients²¹ and patients

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This study was funded by the University Hospital of Montpellier, via the *Contrat Equipe Performante* Funds.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 14, 2019; revised June 3, 2019; accepted for publication June 9, 2019.

Available online ■■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.06.009>

Abbreviations used

CT- Computed tomography
 DAHD- Drug Allergy and Hypersensitivity Database
 DH- Drug hypersensitivity
 DHR- Drug hypersensitivity reaction
 DPT- Drug provocation test
 DRESS- Drug reaction with eosinophilia and systemic symptoms
 iRCM- Iodinated radiocontrast media
 IDT- Intradermal test
 MDHS- Multiple drug hypersensitivity syndrome
 MPE- Maculopapular exanthema
 NIHR- Nonimmediate hypersensitivity reaction
 PT- Patch test
 SCAR- Severe cutaneous adverse reaction
 ST- Skin test

with lupus,²² or in recent studies addressing its prevalence in electronics health records.^{5,12,23} Certain case series provided *in vivo* (skin tests [STs]; drug provocation tests [DPTs]) and *in vitro* (lymphocyte transformation test) proofs of MDHS in a limited number of patients.^{20,24-28} Previous studies have focused on MDHS patient with severe type IV DHRs, namely, severe cutaneous adverse reactions (SCARs).^{24,28}

The group of Gex-Collet et al²⁵ was the first to suggest 2 and then 3²⁸ subtypes of MDHS in nonimmediate reactions: (1) simultaneous MDHS, in which multiple sensitizations occur against drugs given at the same time; (2) sequential MDHS, in which multiple sensitizations develop to drugs given for the same episode, but in a staggered manner; and (3) distant MDHS, in which symptoms of a new DHR appear when the initial DHR has already disappeared (sometimes years apart).

The aim of the present study was to evaluate retrospectively the frequency and characteristics of documented MDHS in a large drug allergy and hypersensitivity database.

METHODS

Patients were selected from our Drug Allergy and Hypersensitivity Database (DAHD). This historico-prospective cohort includes all the patients who have consulted at our allergy clinic (University Hospital of Montpellier, France) since September 1996 with a clinical history suggestive of DHR and who have completed a tailored drug allergy workup, including a drug allergy questionnaire, ST, and DPTs. Skin prick tests, intradermal tests (IDTs), and patch tests (PTs) were performed and read following European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy^{29,30} and International Contact Dermatitis Research Group (ICDRG) guidelines.³¹ For the purpose of this study, the DAHD was questioned up till February 2018. If ST results were negative or nonavailable and contraindications were absent, DPTs were performed. Clinical histories nonevocative of drug hypersensitivity (DH) (eg, headache and isolated vomiting) are neither listed in the DAHD nor considered for potential allergy workup.

Data for patients having positive test results for at least 2 different drugs were retrieved from the database and their charts were reviewed. Patients were excluded if (1) the DHR was due to a single component contained in 2 different drug formulations or (2) in composed drugs (eg, amoxicillin + clavulanic acid); (3) there was possible cross-reactivity between the responsible drugs (a patient with a suspicion of DHR to penicillin and another one to a cephalosporin not sharing the exact side chain is primarily considered as a

potential cross-reactive patient); (4) the patient had positive but nonstandardized nor validated (ie, possibly irritant) ST results or (5) these STs were followed by a negative DPT result; (6) DPT results with placebo were positive; (7) doubtful tests were repeated and the results were eventually considered negative; (8) a single DHR was associated with 1 or more non—drug-related contact allergies; (9) DPTs elicited subjective manifestations (ie, isolated pruritus, headache, isolated abdominal pain); (10) nonspecific histamine release was suspected (eg, chronic spontaneous urticaria and mastocytosis); (11) desensitization, rather than a diagnostic workup, was performed to meet the urgent therapeutic needs of individual patients (HIV-infected patients, cardiac patients). The included patients were analyzed with respect to demographic characteristics, associated comorbidities, clinical features of the DHR, and type and results of the allergy workup.

The DHR was considered an immediate hypersensitivity reaction if symptoms started within 6 hours of the last exposure. It was considered a nonimmediate hypersensitivity reaction (NIHR) if symptoms started more than 6 hours after the last exposure. Potential drug reaction with eosinophilia and systemic symptoms (DRESS) was evaluated following the RegiSCAR score.³² Anaphylaxis was graded according to Ring and Messmer.³³ Allergic reactions with a specific immunologic mechanism were classified as either type I (IgE-mediated) or type IV (T-cell—mediated) as proven by STs, including PTs.

We considered the 3 subtypes of sensitization proposed by Pichler et al,²⁸ and we applied them for all DHRs, whether immediate hypersensitivity reaction or NIHR.

We listed the most frequent drug class occurrences in our DAHD for monosensitized and multiple-sensitized patients, and performed a chi-square test to evaluate a potential difference between the 2 groups.

All patients gave their informed consent to participate in the study. The study was approved by the Institutional Review Board of the University of Montpellier (2018_IRB-MTP_12-16).

RESULTS

Between September 1996 and February 2018, 9250 patients underwent an allergy workup for 1 or more episodes suggestive of DHR and 1819 unique individuals were tested positive for 1 or more drugs. Two hundred one (11%) patients were identified from the database as having positive test results for at least 2 different drugs. The full records of 9 patients were either not available or contained incomplete data and these patients were not included in the study.

After chart review, 147 patients were found to meet the exclusion criteria (Figure 1). A total of 45 subjects (n = 30 females and n = 15 males; median age, 41.6 years at the time of reaction [range, 16-80 years]) were diagnosed as suffering from MDHS, accounting for 92 DHs. Fourteen patients (31.1%) were atopic, and 1 had a history evocative of chronic spontaneous urticaria. General data from the DAHD are presented in Table I.

The most frequent manifestations in the 81 initial reactions were maculopapular exanthema (MPE) in 21 reactions (25.9%), anaphylaxis in 17 (20.9%), and angioedema and urticaria in 14 (17.3%) and 13 (16%) cases, respectively. This series included 8 SCARs (6 DRESS, 2 acute generalized exanthematous pustulosis). Four patients experienced contact eczema after topical application of corticosteroids (tixocortol, dexamethasone) and antiseptic (chlorhexidine) medication. A fixed drug eruption was

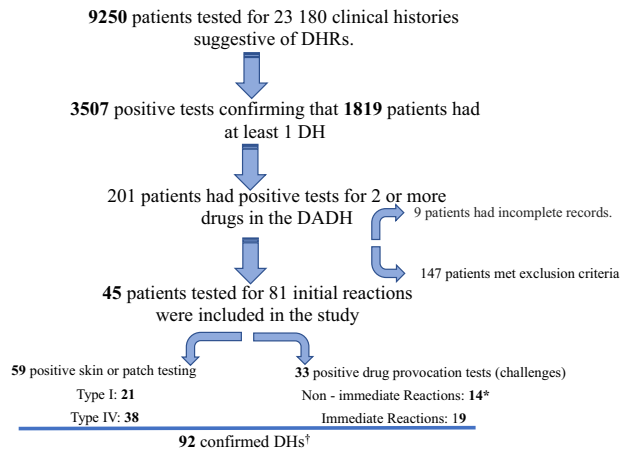


FIGURE 1. Study flowchart. *Patients 7, 13, 42, and 44 have 1 DH diagnosed by means of DPT; considering the clinical picture (patient 42, fixed drug eruption) and/or their context (patient 13, maculopapular exanthema with fever/patients 7 and 44, DRESS and the possibility of MDH during such episodes), these DHs are supposedly type IV DH, even though ST result turned out negative. †The gap of 11 (namely, 92 – 81 = 11) between the number of clinical histories and the number of DHs is explained by 2 factors: some of the patients were sensitized to several drugs during the same initial reaction. They are patients 1, 2, 7, 11, 13, 18, 32, and 44 counting twice with a triple DH. In addition, patients 9 and 4 are peculiar cases explained in the text.

elicited by piroxicam; in 3 cases, the initial reaction was unknown. Two of the 92 DHs were discovered during testing, and 9 patients reported only 1 initial reaction related to different drug classes.

Demographic and clinical characteristics and allergy workup conclusions of the cohort of patients with MDHS are described in Table II. The most frequent culprit drug classes were antibiotics, namely, β -lactam and quinolones, accounting for 37 (40.2%) and 10 (10.8%) DHs, respectively, followed by nonsteroidal anti-inflammatory drugs and iodinated radio-contrast media (iRCM), responsible for 9 (9.8%) DHs each. Fifty-nine diagnoses were made by means of positive ST results (45 skin prick test or intradermal test [IDT] and 14 PT), accounting for 21 type I and 38 type IV DHs (Figure 1). β -Lactam and iRCM were the most frequent elicitors of positive ST results. The diagnosis was confirmed in the remaining 33 cases (of which 9 were for nonsteroidal anti-inflammatory drugs and 10 for quinolones) by means of DPT and for this subgroup, 19 DHs were immediate and 14 were nonimmediate.

Some of the cases we thought were peculiar are detailed below.

Patient 4 had a grade IV anaphylaxis during a computed tomography (CT) scan with iRCM. Along with iRCM we systematically tested chlorhexidine because of its large use in local asepsis. Both ST result and serum specific IgE to chlorhexidine were positive.

In 2008, patient 7 was treated for a respiratory infection by cefpodoxime. Three weeks later he took pristinamycin (a streptogramin/synergistin available in France as tablets) for a dysentery and got an injected (iRCM) CT scan. Two days later, he experienced a DRESS (RegiSCAR score 5). Five years later, he was hospitalized for a pneumothorax and had 2 injected CT scans and multiple antibiotherapies for an infection including pristinamycin, aztreonam, and vancomycin and went through a possible DRESS (RegiSCAR score 2-3) (For both episodes, pristinamycin had been taken for 2 days before the occurrence of the DRESS. This chronology was considered as noncompatible and the drug was therefore tested in DPT.). Skin test results for iRCM came back positive but those for aztreonam (IDT), vancomycin (IDT), and pristinamycin (PT) were negative. We

TABLE I. Characteristics of the 9,250 tested patients and their 23,180 tested CHs

Characteristic	Explored patients and CHs with alleged DH	Patients with 1 confirmed DH	Patients with confirmed MDHS	P value*
Total patients	n = 9,250	n = 1,774	n = 45	
Sex, n (%)				.9
Female	6,321 (68.3)	1,198 (67.5)	30 (66.6)	
Male	2,929 (31.7)	576 (32.5)	15 (33.3)	
Age (y), mean	44.1	47	41.6	
Total CHs	n = 23,180	n = 1,774	n = 92	.001
Time of reaction after the last intake, n (%)				
<6 h	11,046 (47.6)	1,112 (62.7)	40 (48.9)	
>6 h	6,113 (26.4)	517 (29.1)	52 (56.5)	
Unknown	6,021 (26)	145 (8.2)	0	
Severity of reaction				.00004
Anaphylaxis	6,260	955	17	
Nonimmediate severe reactions†	748	47	8	
Other	16,172	772	67	
Average delay reaction-test	299.7 mo	43 mo	76.9 mo	
Average no. of CHs/patients	2.5	3.1	2	

CH, Clinical history.

* χ^2 test was performed between DH and MDHS groups.

†This subgroup includes not only SCARs but also reactions with severity signs that do not reach full criteria of SCARs.

TABLE II. Patients with MDHS

No.	Sex	Age (y)	Atopy	CSU	Suspected drugs	Type of reaction and delay (after the first day of treatment, and after the last ingested dose)	Type and delay in positive test results	Drug class confirmed as DHs	Mechanism
1	M	34	Y	N	Penicillin V Atovaquone	D4, ND D4, ND	DRESS 1-2 PT 72 h PT 72 h	Penicillin Naphthoquinone	NIHR NIHR Type IV Type IV
2	M	80	N	N	Dexamethasone Tobramycin	D2, 6-24 h D2, 6-24 h	Eczema PT 72 h PT 72 h	Corticoid Aminoside	NIHR NIHR Type IV Type IV
3	F	43	N	N	Cefazolin Clindamycin	D1, <1 h D1, <1 h	Ana III Ana III ST <1 h ST <1 h	Cephalosporin Lincosamide	IHR IHR Type I Type I
4	M	70	Y	N	IRCM (Iomeprol) Chlorhexidine	D1, <1 h	Ana IV ST <1 h ST + sIgE <1 h	IRCM Chlorhexidine	IHR IHR Type I Type I
5	F	73	N	N	IRCM (Iobitridol) Piperacillin/tazobactam	D1, 6-24 h D2, ND	MPE MPE ST >24 h ST >24 h	IRCM Penicillin	NIHR NIHR Type IV Type IV
6	F	43	N	N	Pristinamycin Amoxicillin	D1, <1 h D1, <1 h	Ana III Ana III ST <1 h ST <1 h	Streptogramin Penicillin	IHR IHR Type I Type I
7	M	50	N	N	Pristinamycin IRCM (Iopromide)	D2, 6-24 h D2, >24h	DRESS >5 DPT >24 h ST D8	Streptogramin IRCM	NIHR NIHR ND/Type IV Type IV
8	M	73	N	N	Pristinamycin Oxacillin	D1, 1-6 h D2, ND	AGEP MPE PT 72 h ST <1 h	Streptogramin Penicillin	NIHR IHR Type IV Type I
9	F	60	N	N	Amoxicillin Cefuroxime	D5, 6-24 h	DRESS 2-3 None (see text) ST D7 ST <1 h	Penicillin Cephalosporin	NIHR IHR Type IV Type I
10	F	69	N	N	Phenindione Fluindione IRCM (Iodixanol)	ND, >24h ND, >24h ND, >24h	MPE (DRESS?) DRESS >5 PT 72 h ST D7	Vitamin K antagonists IRCM	NIHR NIHR Type IV Type IV
11	M	48	N	N	Piperacilline/tazobactam IRCM (Iopromide)	D20, ND D4, >24h	DRESS 2-3 ST D7 ST D7	Penicillin IRCM	NIHR NIHR Type IV Type IV
12	F	44	N	N	Penicillin Spiramycin	ND, ND D2, ND	Ana II U ST <1 h ST <1 h	Penicillin Macrolide	IHR IHR Type I Type I
13	M	57	N	N	Piperacillin/tazobactam Ciprofloxacin	D20,6-24 h D8, 6-24 h	MPE + fever ST D7 DPT 1-6 h	Penicillin Quinolone	NIHR NIHR Type IV ND/Type IV
14	F	57	N	N	IRCM Penicillin	D1, 1-6 h ND, ND	MPE Angioedema ST D5 ST D7	IRCM Penicillin	NIHR NIHR Type IV Type IV
15	F	48	N	Y	Amoxicillin + Clav acid Spiramycin/metronidazole*	D1, <1 h D1, <1 h	Ana II U ST <1 h DPT <1 h	Penicillin Macrolide/imidazole	IHR IHR Type I ND

16	F	48	N	N	Ceftriaxone Levofloxacin	D1, <1 h D1, <1 h	Ana II U	ST <1 h DPT <1 h	Cephalosporin Quinolone	IHR IHR	Type I ND
17	F	40	N	N	Penicillin Moxifloxacin	ND, ND D2, >24h	MPE MPE	ST >24 h DPT 1-6 h	Penicillin Quinolone	NIHR NIHR	Type IV ND
18	F	16	Y	N	Cefotiam Acetylsalicylic acid	D1, <1 h D1, <1 h	Ana II	ST <1 h DPT 1-6 h	Cephalosporin NSAID	IHR IHR	Type I ND
19	F	38	N	N	Pholcodine Tiaprofenic acid	D1, <1 h D1, 1-6 h	U Angioedema	DPT 1-6 h DPT 1-6 h	Opioid NSAID	IHR IHR	ND ND
20	F	34	N	N	Tixocortol Amoxicillin + Clav acid	D1, 1-6 h D2, 6-24 h	Eczema MPE	PT >24 h ST >24 h	Corticoid Penicillin	NIHR NIHR	Type IV Type IV
21	M	31	Y	N	Penicillin Acetylsalicylic acid	D1, <1 h D1, <1 h	Angioedema Angioedema	ST <1 h DPT 1-6 h	Penicillin NSAID	IHR IHR	Type I ND
22	M	68	Y	N	Penicillin Acetylsalicylic acid	ND, D1 D1, 6-24 h	MPE Angioedema	ST <24 h DPT <24 h	Penicillin NSAID	NIHR NIHR	Type IV ND
23	F	40	N	N	Amoxicillin Neomycin	ND, ND D2, ND	Angioedema Angioedema	ST >24 h ST >24 h	Penicillin Aminocide	NIHR NIHR	Type IV Type IV
24	F	37	ND	N	Ibuprofen Ampicillin	D3, 6-24 h D18, ND	Angioedema MPE	DPT 1-6 h ST >24 h	NSAID Penicillin	IHR NIHR	ND Type IV
25	F	53	Y	N	Spiramycin Amoxicillin	ND, 6-24 h ND, 6-24 h	U U	DPT <24 h DPT <24 h	Macrolide Penicillin	NIHR NIHR	ND ND
26	M	50	N	N	Amoxicillin + Clav acid Tixocortol	D1, <1 h D2, 6-24 h	Ana III Eczema	ST <1 h PT >24 h	Penicillin Corticoid	IHR NIHR	Type I Type IV
27	M	58	ND	N	Carbamazepine Amoxicillin	D46, ND D10, >24h	MPE MPE	PT >24 h ST >24 h	Anticonvulsants Penicillin	NIHR NIHR	Type IV Type IV
28	M	33	Y	N	Acetylsalicylic acid Penicillin	D1, 1-6 h ND, ND	Ana II U	DPT 1-6 h ST <1 h	NSAID Penicillin	IHR IHR	ND Type I
29	F	52	N	N	Penicillin Ciprofloxacin	D1, 1-6 h D2, 6-24 h	Angioedema Angioedema	DPT 1-6 h DPT <24 h	Penicillin Quinolone	NIHR NIHR	ND ND
30	F	35	Y	N	Ofloxacin Penicillin V	D1, <1 h D3, ND	U MPE	DPT 1-6 h ST <1 h	Quinolone Penicillin	IHR IHR	ND Type I
31	F	30	N	N	Amoxicillin + Clav acid Dihydroergotamine	D1, <1 h D1, <1 h	Angioedema Ana II	DPT <1 h DPT 1-6	Penicillin Ergotamine	IHR IHR	ND ND
32	F	32	Y	N	Amoxicillin + Clav acid Spiramycin	D3, >24 h D2, 1-6 h	AGEP	ST >24 h PT 72 h	Penicillin Macrolide	NIHR NIHR	Type IV Type IV
33	M	41	Y	N	IRCM (Iohexol) Penicillin	D1, <1 h ND, ND	Ana II ND	ST <1 h DPT <1 h	IRCM Penicillin	IHR IHR	Type I ND
34	F	78	ND	N	IRCM (Iohexol) Chlorhexidine	D2, >24 h D2, >24 h	MPE Eczema	DPT >24 h PT >24 h	IRCM Chlorhexidine	NIHR NIHR	ND Type IV

(continued)

TABLE II. (Continued)

No.	Sex	Age (y)	Atopy	CSU	Suspected drugs	Type of reaction and delay (after the first day of treatment, and after the last ingested dose)		Type and delay in positive test results	Drug class confirmed as DHs	Mechanism	
35	F	72	N	N	Amoxicillin + Clav acid Moxifloxacin	D3, 6-24 h D2, ND	MPE Angioedema	ST >24 h DPT <1 h	Penicillin Quinolone	NIHR IHR	Type IV ND
36	F	50	N	N	Ceftriaxone Ofloxacin	D1, <1 h D1, <1 h	U U	DPT <1 h DPT <1 h	Cephalosporin Quinolone	IHR IHR	ND ND
37	F	42	Y	N	Paracetamol Amoxicillin	D1, 1-6 h D1, 1-6 h	U Angioedema	DPT <1 h ST <1 h	Paracetamol Penicillin	IHR IHR	ND Type I
38	F	35	Y	N	Roxithromycin Ofloxacin Amoxicillin + Clav acid	D1, 6-24 h D1, ND D1, 6-24 h	U U Ana II	DPT <24 h DPT <24 h ST <1 h	Macrolide Quinolone Penicillin	NIHR NIHR IHR	ND ND Type I
39	F	19	N	N	Amoxicillin + Clav acid Niflumic acid	D2, 6-24 h D2, 6-24 h	MPE MPE	ST <24 h DPT <24 h	Penicillin NSAID	NIHR NIHR	Type IV ND
40	F	33	Y	N	Ofloxacin Amoxicillin + Clav Acid	D1, <1 h D1, <1 h	Ana II ND	DPT <1 h ST <24 h	Quinolone Penicillin	IHR NIHR	ND Type IV
41	F	44	N	N	Penicillin Tixocortol	D2, 6-24 h D1, 1-6 h	MPE MPE	ST <24 h PT D5	Penicillin Corticoïde	NIHR NIHR	Type IV Type IV
42	M	70	N	N	Carbamazepine Piroxicam	D6, 6-24 h D2, 6-24 h	MPE FDE	PT 72 h DPT D2	Anticonvulsants NSAID	NIHR NIHR	Type IV ND/Type IV
43	F	62	N	N	Levofloxacin Acetylsalicylic acid	D1, <1 h ND, ND	Ana III Angioedema	DPT <1 h DPT <1 h	Quinolone NSAID	IHR IHR	ND ND
44	F	79	N	N	IRCM (Iomeprol) Piperacilline/tazobactam Metronidazole	D2, >24 h D25, ND D25, ND	DRESS 2-3	ST D7 ST D7 DPT >24 h	IRCM Penicillin Imidazoles	NIHR NIHR NIHR	Type IV Type IV ND/Type IV
45	M	62	Y	N	Iodopovidone Chlorhexidine	ND, ND D1, <1 h	ND Ana III	PT 72 h ST + sIgE <1 h	Iopovidone Chlorhexidine	NIHR IHR	Type IV Type I

AGEP, Acute generalized exanthematous pustulosis; Ana, anaphylaxis; Clav, clavulanic; CSU, chronic spontaneous urticaria; F, female; FDE, fixed drug eruption; I, immediate; IHR, immediate hypersensitivity reaction; M, male; N, no; ND, not determined; NI, non-immediate; NSAID, nonsteroidal anti-inflammatory drug; sIgE, specific IgE; U, urticaria; Y, yes.

The sign } indicates simultaneous DHs.

TABLE III. Most frequent drug hypersensitivities in the DAHD

Drug class	Explored DH (total = 23,180)	Patient with 1 confirmed DH (n = 1,774)	Patients with MDHS (n = 92)	P value
Penicillins	4,996 (21.5)	741 (41.7)	32 (34.8)	.0001
iRCM	1,806 (7.8)	162 (9.1)	9 (9.8)	
Cephalosporins	1,253 (5.4)	110 (6.2)	5 (5.43)	
NSAIDs	1,282 (5.5)	342 (19.2)	9 (9.8)	
Macrolides	705 (3)	22 (1.2)	5 (5.43)	
Quinolones	406 (1.7)	51 (2.9)	10 (10.8)	
Anti-convulsants	100 (0.43)	4 (0.22)	2 (2.17)	
Aminoglycosides	18 (<0.1)	3 (0.16)	2 (2.17)	
Chlorhexidine	32 (0.13)	12 (0.66)	3 (3.2)	
Other	12,582 (54.3)	327 (18.4)	15 (16.3)	

DH, Drug hypersensitivity; iRCM, iodinated radio-contrast media; MDH, multiple drug hypersensitivity; NSAIDs, nonsteroidal anti-inflammatory drug. Values are n (%).

decided to pursue the allergy workup with a DPT to pristina-mycin with incremental doses over several weeks (starting with 1% of the daily therapeutic dose). He presented a nonsevere MPE 24 hours after the second intake of 10% of the daily therapeutic dose.

Patient 9 was explored after a possible DRESS with amoxicillin. ST results for amoxicillin and ampicillin only were positive at day 7, proving her type IV sensitization to the aminopenicillin side chain. Three months later, she underwent a DPT with cefuroxime (with weekly dose increments, starting at 1% of the daily therapeutic dose) to find an alternative treatment among β -lactams. Immediately after the third intake of the drug (equivalent to 50% of daily therapeutic dose, ie, 500 mg cefuroxime), she presented grade II anaphylaxis with urticaria, vomiting, and dyspnea. Skin test was repeated for cefuroxime and the result became positive in immediate reading, demonstrating IgE-mediated anaphylaxis to this drug, as a distinct allergy from his type IV allergy to the aminopenicillin side chain.

Patient 10 reported a severe MPE (probably a DRESS, but we lacked proper information to diagnose it retrospectively) in 1973 after phenindione intake. In 2007, she was accidentally administered another vitamin K antagonist, namely, fluindione, and experienced a DRESS (RegiSCAR score > 5). At the time, she had iRCM CT scan for the follow-up of her cardiac condition. In 2013, she reported another MPE after a CT scan with iRCM and was tested positive for both fluindione and iRCM.

Two patients, 38 and 44, had confirmed DHs to 3 different drugs. Patient 38 was explored for 3 different episodes with a penicillin, a macrolide, and a quinolone, respectively. Patient 44 was treated for a necrotizing fasciitis with the combination piperacillin/tazobactam and metronidazole. Simultaneously she had repeated CT scans with iRCM. She experienced possible DRESS (RegiSCAR score 2-3). She was given amoxicillin later on by her general practitioner before allergy workup could be performed for her initial episode and developed a nonimmediate MPE. She was tested 15 months later; IDT results were positive at day 7 for penicillin and iRCM. The result for a DPT with metronidazole was positive at 24 hours (nonsevere MPE). Imidazoles were tested because they were deemed important medication for her comorbidities.

Regarding immunologically mediated DHs, only 10 patients (22.2%) combining 21 DHs met the criteria of MDH through

simultaneous sensitization (patients 1, 2, 4, 7, 10, 11, 13, 18, 32, and 44) with 14 type IV, 3 type I, and 4 DHs of undetermined mechanism (ie, proven by positive DPT result, although a genuine type IV mechanism could be easily suspected in all patients, ie, patients 7, 13, 42, and 44). The other MDHSs are distant forms.

Drug class occurrences in the 92 DHs of patients with MDHS seem to differ (Pearson χ^2 P = .0001) from those in mono-allergic patients as presented in Table III. However, further analysis could not be performed because of lack of statistical power in our cohort. The most frequent class associations are presented in Figure E1 in this article's Online Repository at www.jaci-inpractice.org.

DISCUSSION

There are many false assumptions regarding drug allergy. Patients or their physicians frequently report multiple DHRs, most of which have not been confirmed by an allergy workup and this leads to damaging consequences on the quality of medical care.³⁴ Furthermore, it has been demonstrated that the allergy label to antibiotic induces reserve antibiotic utilization³⁵ and has a negative impact on microbial antibiotic resistance.³⁶ This generates significant socioeconomic overhead costs^{37,38} and proves the necessity of allergy workup and delabeling.^{39,40} In our experience (unpublished data) and the experience of others,²⁰ between 20% and 30% of patients consulting for drug allergy report MDHS.

After literature review, in documented DHs the prevalence of MDHS ranges from 0.6% to 2.5% in patients consulting for DH^{20,27} to 10% to 18% in selected patients with SCARs, especially with DRESS.²⁴ Incomplete recurrences (cutaneous involvement but without organ involvement) with structurally unrelated drugs are a frequent phenomenon (25%) in DRESS.⁴¹ Considering both immediate and nonimmediate reactions, our results are concordant with these observations and confirm that genuine MDH is a very rare condition, concerning about 2.5% of patients with a confirmed DHR and 0.5% of the population with self-reported DHs consulting in our unit.

Although our series of patients is too small to allow a proper risk factor search, some observations can be made. Subtypes of simultaneous and sequential MDHS have clearly been associated with SCARs, especially DRESS, and risk factors have been

suggested, such as the type of drug, high or recently increased drug dosages, and long-lasting treatment.²⁸ In our study, only 8 patients (patients 1, 7, 8, 9, 10, 11, 32, and 44) had an initial SCAR. In this subgroup, the drug exposure period ranged from 1 to 25 days before the DH occurrence. They were all inpatients, hospitalized for severe infections. Whenever an iRCM was involved (patients 7, 10, 11, and 44), the patient had had simultaneous and multiple exposures to this class, during a short lapse of time (range, 7 days–3 weeks). Six of 8 patients had simultaneous MDHS, mostly for β -lactams. *In vitro* studies^{10,11,42} on drug-reactive T cells from MDHS versus monoallergic patients (and controls) found that the first had persistent T-cell activation accounted for by a subset of CD4⁺CD25^{dim}, CD38⁺, and PD-1⁺ T cells. This persistent stimulation could be related to subsequent development of further DH to new drugs. If HLA-driven susceptibility to individualized DHRs has been demonstrated,⁴³ with variable clinical relevance in daily practice, there is no such proof so far for MDHS, even in high-risk patients, such as patients having suffered from SCAR. Little is known however about other forms of MDHS (eg, mixing immediate and nonimmediate DHRs), which might seem “coincidental” at first sight (ie, patients cumulating frequent DHRs). Blanca-López et al⁴⁴ found that patients with confirmed DHR to β -lactams had an increased risk of confirmed quinolone DH. In our study, the association of β -lactams/quinolone DH was found in 9 of the 10 patients with a quinolone DH. In our experience with antibiotic DH, this risk factor could not be reproduced.

In most cases of multiple reactions to β -lactams, cross-reactivity by means of a common structure is involved, which made multiple sensitizations to different β -lactams an extremely rare phenotype,^{10,45} as presented by our patient 9.

Although simultaneous sensitization is classically a “prerogative” of NIHR, 2 patients (4 and 18) in our series had positive test results for 2 distinct drugs given in the context of an immediate hypersensitivity reaction. These cases are anecdotal in the literature²⁰ and could hardly be explained by a concrete immunologic support as for simultaneous NIHR and may as well be coincidental.

We acknowledge that our study has several limitations. According to allergy workup recommendations, not all suspicions of DH are to be tested, and indications as well as contraindications are to be observed.²⁸ Therefore, we might have underestimated the prevalence of MDHS in our population by choosing not to test certain alleged DHRs. We tested only those drugs that are mandatory for patient’s health care. Hence, antibiotics such as β -lactams or quinolones are overrepresented in our allergic patients, whereas macrolides or aminoglycosides are less often explored. We mostly performed *in vivo* tests (with rare exceptions, where serum specific IgE levels were commercially tested). Performing complementary *in vitro* tests (eg, lymphocyte transformation test) could have given us additional insight into the pathomechanisms of this condition, especially in patients with severe DHRs, in whom DPT is contraindicated. Because MDHS is rare, we made the choice to include in this series all the cases from our database fulfilling the established inclusion criteria, rather than just to refer to well-characterized phenotypes, such as NIHR MDHS.²⁶

Our study adds knowledge to the few reports on patients with MDHS. We agree with Ayuso et al¹⁷ that further studies

(potentially multicenter) associating *in vivo* and *in vitro* testing are needed to better characterize these patients.

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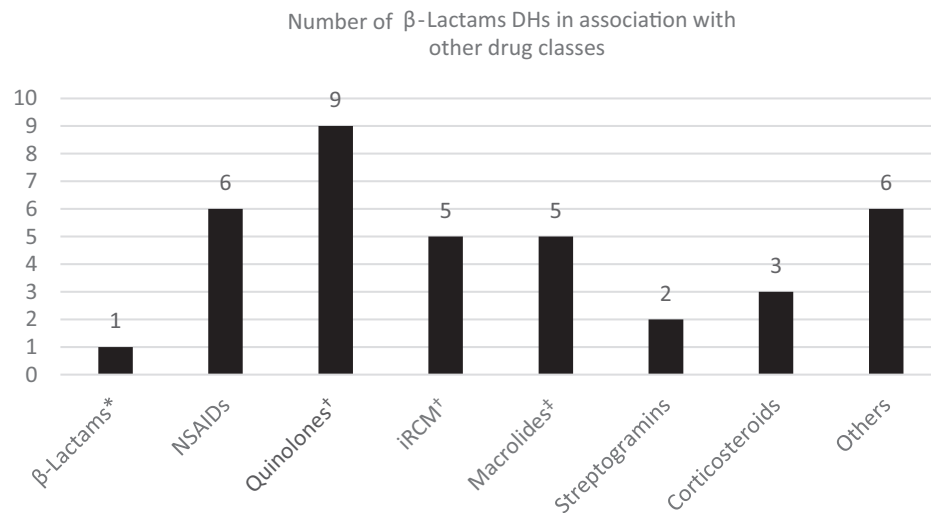


FIGURE E1. Most frequent drug associations in patients with MDHS in our series. *NSAID*, Nonsteroidal anti-inflammatory drug. Total β -lactams associations $n = 37$. *Patient 9 with 2 distinct DHs to β -lactams. †Two patients have triple DHs. ‡In patient 15, macrolide is in association with an imidazole.