Drug-induced hypersensitivity reactions in a Lebanese outpatient population: A decade-long retrospective analysis (2012-2021)

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Background: Drug hypersensitivity reactions (DHRs) are becoming more common as a result of increasing prevalence and case complexity. Allergists and clinical immunologists worldwide are challenged daily to adequately diagnose and manage these reactions. Data in the literature regarding DHR outpatient consultations are scarce worldwide, limited in the Middle East, and currently unavailable in Lebanon.

Objective: This retrospective study aimed to evaluate the characteristics of all reported DHRs over 10 years in a tertiary-care allergy clinic in Lebanon.

Methods: We conducted a decade-long (2012-21) retrospective analysis of the archived medical records of patients with a history of DHRs. Demographics, clinical history, diagnostic tools, and characteristics of the DHRs were collected and analyzed.

Results: A total of 758 patients experienced DHRs to therapeutic molecules provided for ambulatory care. Our results identified 72 medications. The most frequently implicated drug classes included β-lactam antibiotics (53.8%), followed closely by nonsteroidal anti-inflammatory drugs (48.9%). Of the 758 patients, 32.6% reported DHRs to multiple molecules, and 11.8% reported concomitant DHRs to 1 or several molecules provided in the perioperative setting. Of those, opioids and neuromuscular blocking agents were the 2 most common therapeutic classes. Furthermore, we evaluated the cross-reactivity between molecules of the same class. In neuromuscular blocking agents, rocuronium and cisatracurium were the most commonly cross-reactive, and for opioids, the most common association we recorded was with morphine and pethidine.

Conclusion: Our findings constitute the first step toward a more comprehensive evaluation of the clinical characteristics of DHRs in Lebanon. (J Allergy Clin Immunol Global 2024;3:100169.)

Key words: *Drug hypersensitivity reaction, drug allergy, epidemiology, outpatient clinic, Lebanon, β-lactams, nonsteroidal anti-inflammatory drugs, opioids, neuromuscular blocking agents*

Drug hypersensitivity reactions (DHRs) are idiosyncratic, unpredictable dose-independent adverse drug reactions.[1-3] They represent 15% to 20% of adverse drug reactions and are potentially life-threatening.[4-7] Therefore, DHRs are a frequent reason for consultation in allergy clinics:[8,9] they are responsible for high morbidity and mortality, constituting a significant burden on health care resources.[10-12]

DHRs are classified as immediate or delayed. Immediate reactions can be allergic or nonallergic. Allergic reactions occur when a specific adaptive immune response is involved.[9,13] Immediate allergic reactions are typically mediated by specific IgE and usually arise less than 1 hour after exposure.[14] However, some immediate responses may appear up to 6 hours after administration, especially if the drug has been administered orally and after food intake, which slows its absorption.[2] Delayed-onset reactions can occur more than 1 hour to a few days after the initial administration of the drug and are mediated by $CD4^+$/$CD8^+$ T lymphocytes.[15,16] When mediated by $CD8^+$ T lymphocytes, DHRs are generally severe cutaneous adverse reactions.[17-19] However, other organs and tissues may be involved, such as the kidneys, liver, heart, and blood.[20] The mechanisms of action of nonallergic reactions (or pseudo-allergies) are numerous and depend on the molecules studied. They are mediated by the release of mediators from basophils and mast cells that are not triggered by IgE.[13] One of the mechanisms described, notably with fluoroquinolones and neuromuscular blocking agents (NMBAs), is the direct binding to Mas-related G protein–coupled receptor X2 (aka MRGPRX2) on the surface of mast cells, which triggers their degranulation and the release of mediators such as tryptase and histamine that are responsible for the reaction.[21,22]

Most DHRs appear after the administration of antibiotics, particularly β-lactams (BLs), nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, antigout agents, NMBAs, chemotherapy, and radiocontrast media (RCM).[23] The threat of developing DHRs increases in people with risk factors, such as family and personal history or polymorphism of the major histocompatibility complex.[24]

Due to the increase in DHRs, it is a real challenge for physicians to properly diagnose and manage these reactions.

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Abbreviations used

AAAAI: American Academy of Allergy, Asthma & Immunology
aDHR: Active DHR
BL: β-Lactam
COVID-19: Coronavirus disease 2019
DHR: Drug hypersensitivity reaction
HDF: University Medical Center Hôtel-Dieu de France
NMBA: Neuromuscular blocking agent
NSAID: Nonsteroidal anti-inflammatory drug
RCM: Radiocontrast media
SJS: Stevens-Johnson syndrome
SPT: Skin prick test
TMP/SMX: Trimethoprim/sulfamethoxazole

A false allergy diagnosis based solely on medical history may limit patients' treatment options and lead to using less effective, more dangerous, or more expensive drugs.[25] Additionally, a reported allergy to one drug may falsely suggest that the patient is allergic to all medications in the same therapeutic class.[14] The current diagnostic approach for DHRs is based on a complete clinical history, eventually leading to an allergy workup with standardized skin tests, biological and occasionally *in vitro* tests, and finally, drug provocation tests, which is the last step for accurate diagnosis of DHRs.[26,27]

Several epidemiology reports study DHRs. Each differs according to the population studied (hospitalized patients, patients seen in general practice clinics or the emergency departments, children or adults), the methodology used (diagnosis based solely on clinical history, skin testing, or biological testing), and the drugs implicated. Furthermore, epidemiological data on DHRs in nonhospitalized patients are scarce and are limited mainly to antibiotics.[28-32] There are few publications on drug-allergic outpatients worldwide, and only a few of those previously published were located in the Middle East.[33-35] In addition, Lebanon's geographical location and social characteristics have impacted the population's genetic diversity, leading to the identification of numerous distinct genetic particularities.[36-39] We conducted this retrospective study in an allergist practice to evaluate the clinical characteristics and diagnostic workup of reported DHRs in Lebanon over 10 years.

METHODS

Study design

We conducted a decade-long (2012-2021) retrospective review of patients' physical and electronic archived medical records with a positive history of DHR. These patients were referred to the outpatient allergy clinic at the University Medical Center Hôtel-Dieu de France (HDF) hospital in Beirut, which is considered a tertiary-care allergy clinic in Lebanon. The Lebanese health care system is concentrated in the capital, Beirut. Consequently, this clinic welcomes patients from across the Lebanese territory. These patients were transferred from HDF or other hospitals, needing follow-up or referred by other physicians.

The clinic's medical records were used as the data source. In 2018, an electronic International Organization for Standardization–certified telemedicine platform, TrakMD, was introduced. All paper medical records from 2012 to 2017 and electronic documents from 2018 to 2021 were studied. Data collection was performed anonymously by assigning an identification number to each patient. All data collected were obtained solely for research reasons. This study was approved by the HDF ethical committee (case CEHDF 1598).

Demographic information, study variables, and analysis

Our study's primary objective and main inclusion criteria were to identify and evaluate all patients with DHRs to therapeutic molecules provided during ambulatory care, so therefore, by definition, they were not hospitalized (758 patients). Moreover, 190 of these patients experienced, in addition to their DHRs in ambulatory care, a reaction to 1 or more molecules provided in the perioperative setting. These were described separately. We excluded patients with exclusive reactions to medications provided in the perioperative setting.

Every patient underwent a physical examination, and a standardized questionnaire was completed. Blood and skin tests were then prescribed when they were applicable. Demographics, clinical history, diagnostic tools, and specific characteristics of the DHRs were collected and analyzed for all individuals. The following data were recorded for each subject: age at the time of consultation, sex, reason for consultation, urgency of consultation, date of visit, medical history, relevant family history, food allergies, respiratory allergies, drugs responsible for the DHRs, type and symptom of reaction, skin tests, and biological diagnostic investigations.

Data were entered into 2019 Microsoft Excel (Microsoft, Redmond, Wash) and exported to GraphPad Prism v8.0.0 (GraphPad Software, La Jolla, Calif) for analysis. The results of the descriptive analysis are presented as numbers and percentages of patients for each variable.

Skin prick test

Skin prick tests (SPTs) were performed according to American Academy of Allergy, Asthma & Immunology (AAAAI) guidelines. For antibiotics of the penicillin family, a diagnostic kit (Diater, Madrid, Spain) was used. This kit contains 0.04 mg of benzylpenicilloyl poly-L-lysine and a minor determinant mix consisting of 0.5 mg each of benzylpenicillin, benzylpenilloate, and benzylpenicilloate. Pure poly-L-lysine and minor determinant mix prick testing was performed per the manufacturer's recommendation. The investigation of amoxicillin, latex, patent blue, and RCM was performed by SPT using commercial extracts following the manufacturer's guidelines. Other molecules (including drugs provided in the perioperative setting) were all provided by the pharmacy or the operating room of the HDF hospital. These SPTs were conducted at full concentration using a crushed pill or powder for intravenous solution dissolved extemporaneously before testing in 2 mL of purified water. The test was performed via a prick to the skin of the forearm with a Stallerpoint lancet (Stallergenes Greer, Baar, Switzerland). The results were read 15 minutes later, with close monitoring. Patients were advised to stop all antihistamine medications 5 days before testing. The SPT results were considered positive when a wheal and flare reaction of ≥3 mm was observed and compared to histamine and saline used as positive and negative controls, respectively. It is important to note that all tests were conducted by

TABLE I. Demographic characteristics of patients with DHRs, 2012-21

Characteristic	Value
Total no. of patients with DHRs included	758
Sex ratio, F:M	2.6:1
Age (years), range (median)	1-87 (39)
Reason for consultation	
aDHR	190 (24.9)
Preanesthesia evaluation	60 (7.9)
Food allergy	26 (3.4)
Respiratory allergy	15 (2.0)
Other symptoms	
Urticaria	147 (19.4)
Rhinitis	86 (11.3)
Angioedema	33 (4.4)
Asthma	31 (4.1)
Dermatitis	29 (3.8)
Chronic cough	25 (3.3)
Rhinosinusitis	14 (1.8)
Pruritis	12 (1.6)
Bronchitis	11 (1.5)
Other*	79 (10.6)
Concomitant history of allergy	262 (34.6)
Respiratory allergy	173 (47.3)
Food allergy	138 (52.7)
Family history of allergy	226 (29.8)
Respiratory allergy	212 (93.8)
Drug allergy	14 (6.2)
DHR to 1 or multiple molecules	
One molecule	511 (67.4)
Two molecules	159 (20.9)
Three molecules	75 (9.9)
Four molecules	11 (1.5)
Five molecules	2 (0.3)

Data are presented as nos. (%) unless otherwise indicated.
*Other includes dyspnea, conjunctivitis, rhinoconjunctivitis, anaphylaxis, alopecia, shortness of breath, contact dermatitis, nasal congestion, nasal polyposis, vasculitis, otitis, pneumonia, bullous lichen planus, bronchitis, psoriasis, and scalp seborrheic dermatitis.

the same operator, thereby enhancing pertinence and reproducibility.

RESULTS

All patients' medical records were retrospectively analyzed, and 758 patients met the study criteria. The characteristics of the study population are shown in Table I. Patients were predominantly female (72.3%), with a female-to-male ratio of 2.6 to 1 and a median age of 39 years. Patients were included if they had been labeled as allergic by the physician, regardless of whether they presented an active DHR (aDHR) in the clinic as the main reason for their consultation. Other patients had different primary reasons for consultation with a history of DHR. Of these 758 patients, 190 constituting almost 25% of cases, were examined by the physician for an aDHR. More than a third (34.6%) had concomitant allergies, including food allergies (52.7%) and respiratory allergies (47.3%). On the other hand, 29.8% had a family history of allergies, including drug allergies (6.2%), and 93.8% had a family record of respiratory allergies. Most patients presented reactions to only 1 drug (67.4%), 20.9% and 9.9% had DHRs to 2 or 3 molecules, respectively, and less than 2% presented reactions to 4 and 5 drugs.

All 758 patients were diagnosed based on detailed clinical history. For the 190 patients presenting an aDHR, the physician prescribed an allergy SPT 4 to 6 weeks later, when necessary for confirmation. SPTs were performed in 22.6% of cases (see Fig E1 in the Online Repository at www.jaci-global.org).

A total of 72 suspected drugs were identified. The most frequently implicated drug classes included BL antibiotics (53.8%), followed closely by NSAIDs (48.9%). Other antibiotics induced fewer cases of DHRs (Fig 1), followed by RCM, opioids, and acetaminophen.

All cases of antibiotic hypersensitivity reactions are represented in Table II. The most common drug class responsible for DHRs in our study was BL (53.8%), including penicillins and cephalosporins. The most commonly implicated active substance was amoxicillin associated with clavulanic acid, which was reported in 168 cases. Other prevalent antibiotics were quinolones (7.8%), sulfonamides (5.8%), and nitroimidazole (3.6%). Fewer cases of macrolides, lincomycin, and tetracycline DHRs were observed. Of all the antibiotic cases reported, 94 were confirmed by SPT, most of which were for BLs. Most patients presented immediate DHRs to antibiotics. The symptoms primarily included urticaria, with or without angioedema, and a few cases of anaphylaxis with BLs, metronidazole, and the association of trimethoprim with sulfamethoxazole (TMP/SMX). We also observed delayed DHRs such as skin rash, including erythema multiforme and dermatitis, and a few cases of Stevens-Johnson syndrome (SJS) and fixed drug eruptions.

Six SJS cases were documented (see Table E2 in the Online Repository at www.jaci-global.org) following TMP/SMX, metronidazole, or allopurinol administration. All patients were above 60 years old and had no family histories of DHRs, concomitant food, or respiratory allergies.

Nonantibiotic DHRs are presented in Table III. Following BLs, the second most commonly found drug class was NSAIDs, responsible for 371 cases of reported DHRs (48.9%). Aspirin was the most frequent in this group (11.9%). Urticaria was again the most frequent symptom, followed by angioedema, anaphylaxis, and skin rash, with mostly immediate reactions (96.2%). Other frequent events included 17 clinically diagnosed RCM cases and 13 opioids for ambulatory use.

Within the evaluated time frame, the evolution of aDHR prevalence for NSAIDs, BLs, and other antibiotics was analyzed (Fig 2). Antibiotic hypersensitivity cases were stable between 2012 and 2016. Then a significant drop occurred between 2016 and 2017, followed by a gradual rise until the end of 2021. However, for NSAIDs, the records were constant between 2012 and 2019, and a 50% rise was recorded until 2021. The highest number of DHR visits were recorded between 2020 and 2021 for all drug classes (31 cases for NSAIDs, 38 for BLs, and 24 for other antibiotics).

We then detailed the characteristics of 90 patients (11.9%) with a history of ambulatory DHRs and concomitant DHRs to 1 or more molecules provided in the perioperative setting (Table IV). All were immediate reactions, and the predominant symptom observed was anaphylaxis, followed by angioedema, dyspnea, and facial erythema. An SPT workup was systematically performed for all patients using a selection of molecules shown in Table V according to the reaction history. Positive reactions to opioids (74 patients), NMBAs (57 patients), hypnotics (18 patients), and local anesthetics (12 patients) were recorded. Thirty-six patients with latex hypersensitivity and 5 patent blue

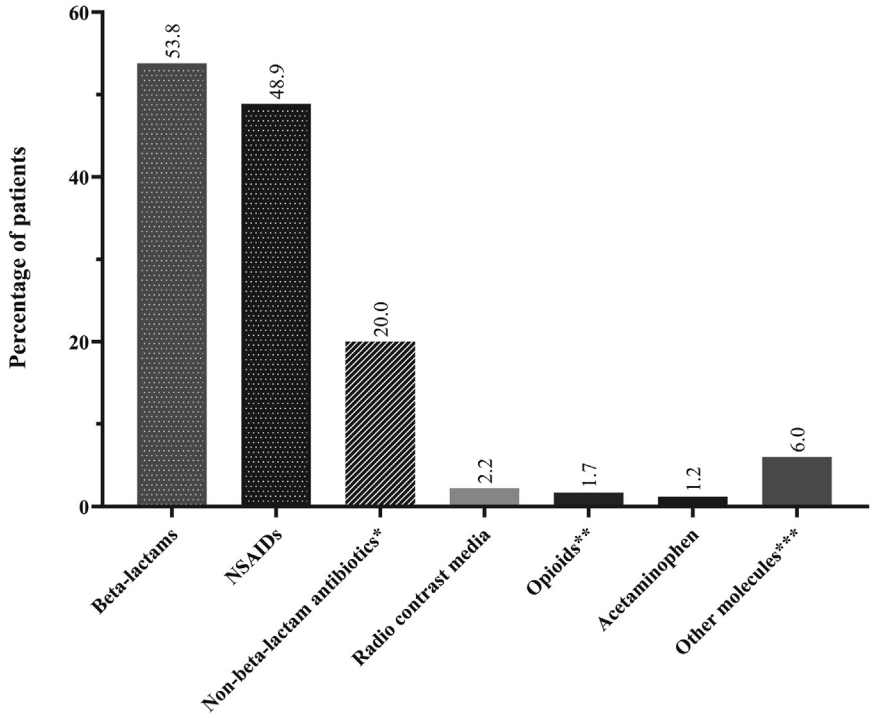

FIG 1. Percentages of the most common drugs implicated in DHRs (n = 758 patients). Molecules provided in the perioperative setting are presented separately in Table IV. Percentages do not add up to 100 because a single patient could report multiple DHRs. *Other antibiotics included quinolones, sulfonamides, metronidazole, macrolides, clindamycin, and tetracyclines. **Opioids in ambulatory cases. ***Other molecules are listed in Table E1, available in the Online Repository at www.jaci-global.org.

hypersensitivity cases were also observed. Morphine was found in 52 occurrences, followed by rocuronium (46 cases).

Results from SPTs allowed us to study cross-reactivity for NMBAs and opioids. Of the 57 patients with positive SPT to NMBAs, we recorded 39 cases of single-agent sensitization, and 15 showed cosensitization to 2 molecules, mostly rocuronium and cisatracurium (n = 10). Positive SPTs to 3 molecules were observed in 3 patients, 2 of which were rocuronium, cisatracurium, and atracurium. Of the 74 patients with a positive SPT to opioids, 49 showed cross-reactivity. The most frequent association of molecules was analyzed. For opioids, 26 were reactive to 2 molecules, majorly to morphine and pethidine, with 13 cases, 13 to 3 molecules (n = 4 to morphine, pethidine, and fentanyl), 9 to 4 molecules (n = 3 to morphine, pethidine, sufentanil, and remifentanil), and 1 case of cross-reactivity to morphine, pethidine, sufentanil, remifentanil, and fentanyl. Hypnotics and local anesthetics showed rare cross-reactivities, with 1 case of cross-reactivity to midazolam and ketamine, 1 case of midazolam, ketamine, and etomidate, and 1 case of lidocaine and ropivacaine (Table VI).

DISCUSSION

Epidemiological studies of DHRs present multiple outcomes mainly due to divergence in study populations. The populations studied are hospitalized inpatients, outpatients, individuals from national databases, pharmacovigilance databases, or ED attendances, thus resulting in varying outcomes.[5,23,40] To our knowledge, these reports are scarce in the Middle East,[33,41-44] and data in the literature regarding drug allergies to molecules provided in ambulatory care is currently unavailable in Lebanon whether the data is obtained from tertiary-care academic medical centers, community physicians or private practices. The primary aim of our study is to provide a comprehensive retrospective analysis of DHRs in an outpatient population, to provide, for the first time, an overview of national DHRs, and to document specific characteristics.

From the 758 patients analyzed, females outnumbered the males, with a female-to-male ratio of 2.6:1. Our results are consistent with those found by others, such as Gamboa and colleagues, who investigated an outpatient Spanish database.[30,45,46] It is still unclear why women are more prone to DHRs. Some reports suggested that this difference was probably due to the higher drug consumption by women compared to men with more repeated exposure to antibiotics/medications, genetic factors, epigenetic changes, or hormonal influences on immune cells.[47-49] The mean age in our study was 39 years. These findings corroborated with evidence published in the literature demonstrating that DHRs in an outpatient population mainly occur in young and middle-aged adults with a mean age of close to 40 years.[30,50,51] However, other studies on hospitalized patients showed an older average.[32]

We showed that BL antibiotics, followed by NSAIDs, were the 2 most implicated drug classes in the recorded DHRs, with a majority of cases associated with amoxicillin/clavulanic acid. Multiple studies showed that BL antibiotics are the most frequent elicitors of DHRs.[52-55] Doña et al recorded 25% to 35% of BL DHRs.[56] These percentages are lower than those recorded in our study (approximately 50%), which might be attributed to the high levels of misuse and over-the-counter delivery of

TABLE II. Characteristics of antibiotic hypersensitivity reactions

Antibiotic class	No. (%)*	Molecules	Clinically diagnosed, no. (%)†	SPT confirmed, no. (%)†	Symptoms (%)†	Delayed/early onset of reaction (%)†
BLs	408 (53.8)	Penicillins				
		Amoxicillin/ clavulanic acid	159 (39.0)	9 (2.2)	● Urticaria (79.2) ● Angioedema (10.8) ● Gastrointestinal (3.2) ● Anaphylaxis (3.2) ● Pruritis (1.4) ● Other (2.2)	● Immediate (95.8) ● Delayed (4.2)
		Penicillin G	116 (28.4)	38 (9.3)		
		Amoxicillin	21 (5.1)	15 (3.7)		
		Ampicillin	2 (0.5)	—		
		Cephalosporins				
		Ceftriaxone	9 (2.2)	—		
		Cefixime	7 (1.7)	3 (0.7)		
		Cefuroxime	6 (1.5)	2 (0.5)		
		Cefdinir	3 (0.7)	—		
		Cefpodoxime	3 (0.7)	2 (0.5)		
		Cefadroxil	2 (0.5)	—		
		Cefalexin	1 (0.3)	—		
		Not specified	8 (2.0)	2 (0.5)		
		Total	337 (82.6)	71 (17.4)		
Quinolones	59 (7.8)	Levofloxacin	24 (40.6)	1 (1.7)	● Urticaria (66.1) ● Angioedema (13.6) ● Skin rash (10.2)‡ ● Other (10.1)	● Immediate (77.8) ● Delayed (22.2)
		Ciprofloxacin	7 (11.9)	9 (15.2)		
		Nadifloxacin	2 (3.4)	—		
		Norfloxacin	2 (3.4)	—		
		Ofloxacin	1 (1.7)	—		
		Not specified	7 (11.9)	6 (10.2)		
		Total	43 (72.9)	16 (27.1)		
Sulfonamides	44 (5.8)	TMP/SMX	44 (100.0)	—	● Skin rash (72.7)‡ ● Urticaria (13.6) ● SJS (6.8) ● FDE (2.3) ● Angioedema (2.3) ● Anaphylaxis (2.3)	● Immediate (77.3) ● Delayed (22.7)
Nitroimidazoles	27 (3.6)	Metronidazole	24 (88.9)	3 (11.1)	● Urticaria (74.1) ● Angioedema (11.1) ● Anaphylaxis (3.7) ● Facial erythema (3.7) ● SJS (3.7) ● Skin rash (3.7)‡	● Immediate (92.6) ● Delayed (7.4)
Macrolides	10 (1.3)	Clarithromycin	2 (20.0)	1 (10.0)	● Urticaria (100.0)	● Immediate (100.0)
		Erythromycin	2 (20.0)	—		
		Azithromycin	1 (10.0)	—		
		Spiramycin	1 (10.0)	—		
		Not specified	2 (20.0)	1 (10.0)		
		Total	8 (80.0)	2 (20.0)		
Lincomycin	9 (1.2)	Clindamycin	7 (77.8)	2 (22.2)	● Urticaria (55.6) ● Skin rash (22.2)‡ ● Tachycardia (11.1) ● FDE (11.1)	● Immediate (55.6) ● Delayed (44.4)
Tetracycline	2 (0.3)	Doxycycline	1 (50.0)	—	● Urticaria (50.0) ● Gastritis (50.0)	● Immediate (50.0) ● Delayed (50.0)
		Not specified	1 (50.0)	—		

Clinically, DHRs are classified as immediate (typically <1 hour after last intake of culprit drug) or delayed (typically >1 hour to days after initiating treatment with culprit drug).[14]
FDE, Fixed drug eruption.
*Percentage of total number of patients in study population.
†Percentage of number of patients in therapeutic class.
‡Skin rash other than urticaria, including erythema multiforme and dermatitis.

TABLE III. Characteristics of nonantibiotic DHRs

Molecule class	No. (%)*	Molecule	Clinically diagnosed, no. (%)†	SPT confirmed, no. (%)†	Symptoms (%)†	Delayed/early onset of reaction (%)†
NSAID	371 (48.9)	Aspirin	44 (11.9)	—	• Urticaria (66.8) • Angioedema (22.4) • Anaphylaxis (2.4) • Skin rash (1.9)‡ • Dyspnea (1.9) • Pruritis (1.1) • Other (3.5)	• Immediate (96.2) • Delayed (3.8)
		Ibuprofen	32 (8.6)	—		
		Diclofenac	15 (4.0)	—		
		Ketoprofen	8 (2.2)	—		
		Mefenamic acid	5 (1.3)	—		
		Aceclofenac	4 (1.1)	—		
		Celecoxib	4 (1.1)	—		
		Etoricoxib	4 (1.1)	1 (0.3)		
		Naproxen	3 (0.8)	—		
		Normocoxib	3 (0.8)	—		
		Lysine clonixinate	1 (0.3)	—		
		Not specified	245 (66.0)	2 (0.5)		
		Total	368 (99.2)	3 (0.8)		
RCM	17 (2.2)	RCM	17 (100.0)	—	• Urticaria (64.7) • Anaphylaxis (23.5) • Angioedema (11.8)	• Immediate (100.0)
Opioids for ambulatory use	13 (1.7)	Tramadol	10 (76.9)	2 (15.4)	• Urticaria (61.5) • Hypotension (23.1) • Angioedema (15.4)	• Immediate (76.9) • Delayed (23.1)
		Codeine	1 (7.7)	—		
		Total	11 (84.6)	2 (15.4)		
Acetaminophen	9 (1.2)	Acetaminophen	9 (2.4)	—	• Urticaria (66.7) • Angioedema (33.3)	• Immediate (100.0)

Clinically, DHRs are classified as immediate (typically <1 hour after last intake of culprit drug) or delayed (typically >1 hour to days after initiating treatment with culprit drug).[14]
*Percentage of total number of patients in study population.
†Percentage of number of patients in therapeutic class.
‡Skin rash other than urticaria, including erythema multiforme and dermatitis.

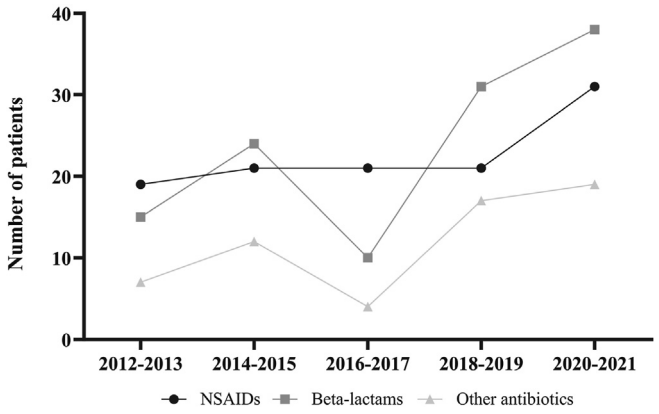

FIG 2. Evolution of number of NSAIDs, BLs, and other antibiotic drug hypersensitivity cases from 2012 to 2021.

antibiotics in Lebanon.[57,58] In fact, Cheaito et al reported that 42% of the population in Beirut and its suburbs are self-medicated with antibiotics,[57] the majority with amoxicillin/clavulanic acid.[59] Furthermore, clavulanic acid might be an increasing source of adverse reactions because of the possibility of developing specific IgE.[60] Another study showed high level of antibiotic misuse among the Lebanese population. In fact, more than a third of the population does not consult a physician before starting the treatment.[61,62] Moreover, given the large number of estimated penicillin allergies that are falsely labeled, allergy assessment and penicillin skin testing are crucial approaches in effectively addressing and clarifying reported penicillin allergies. Specifically, penicillin skin testing stands out as a highly favorable choice due to its ability to ascertain the absence of a positive IgE-mediated reaction with a negative predictive value exceeding 95%.[63,64] Furthermore, in Lebanon, we follow the international guidelines regarding drug allergy diagnosis; in particular the AAAAI practice parameters and the European Academy of Allergy and Clinical Immunology (EAACI) guidelines on drug allergy. Indeed, as allergists, we have found great value in offering the opportunity and accessibility of skin tests for penicillin, as it has been instrumental in effectively disproving penicillin allergies and removing the associated label in Lebanon.

In addition, as recounted by others, NSAIDs were the second most reported DHR in our clinic.[10] NSAIDs can cause immune DHRs, or, more frequently, nonimmune reactions due to the inhibition of cyclooxygenase-1 (COX-1), leading to a shunt of arachidonic acid metabolism toward the 5-lipoxygenase pathway and increased production of cysteinyl leukotrienes. This shunt results in the depletion of prostaglandin E_2 and the release of inflammatory mediators from mast cells and other inflammatory cells.[9,65] Aspirin was the most reported NSAID, followed by ibuprofen

TABLE IV. Overall characteristics of patients with history of ambulatory DHRs and positive SPT test results

Characteristic	No. (%)	SPT confirmed, no. (%)	Clinically diagnosed	Symptoms (%)	Delayed/early onset of reaction (%)
Molecules provided in perioperative setting	90 (11.9)	90 (100.0)	—	● Anaphylaxis (95.6) ● Angioedema (2.2) ● Dyspnea (1.1) ● Facial erythema (1.1)	● Immediate (100.0)

Clinically, DHRs are classified as immediate (typically <1 hour after last intake of culprit drug) or delayed (typically >1 hour to days after initiating treatment with culprit drug).[14]

TABLE V. Number of patients with history of ambulatory DHRs with positive SPT test result to different molecules provided in perioperative setting

Drug class	No. of patients with positive SPT test result	Molecule	No. of cases
Opioids	74	Morphine	52
		Pethidine	38
		Sufentanil	26
		Remifentanil	21
		Fentanyl	18
		Oxycodone	2
NMBA	57	Rocuronium	46
		Cisatracurium	19
		Atracurium	10
		Suxamethonium	3
Hypnotics	18	Midazolam	8
		Ketamine	5
		Propofol	4
		Etomidate	3
		Pentobarbital	1
		Sodium thiopental	1
Local anesthesia	12	Lidocaine	7
		Bupivacaine	3
		Ropivacaine	2
		Mepivacaine	1
Other	39	Latex	36
		Patent blue	5

TABLE VI. Most common associations evaluating possible cross-reactivity to molecules provided in perioperative setting in patients with history of ambulatory DHR

Drug class	No. of molecules	No.	Most frequent molecules*	No.
Opioids	One molecule	25	Morphine	11
	Two molecules	26	Morphine, pethidine	13
	Three molecules	13	Morphine, pethidine, fentanyl	4
	Four molecules	9	Morphine, pethidine, sufentanil, remifentanil	3
	Five molecules	1	Morphine, pethidine, sufentanil, remifentanil, fentanyl	1
NMBA	One molecule	39	Rocuronium	29
	Two molecules	15	Rocuronium, cisatracurium	10
	Three molecules	3	Rocuronium, cisatracurium, atracurium	2
Hypnotics	One molecule	16	Midazolam	6
	Two molecules	1	Midazolam, ketamine	1
	Three molecules	1	Midazolam, ketamine, etomidate	1
Local anesthesia	One molecule	11	Lidocaine	6
	Two molecules	1	Lidocaine, ropivacaine	1

*For each number of molecules, only most frequent association of cross-reactivity is described.

and diclofenac. Our results were consistent with the presence of the heteroaryl acetic acid group in diclofenac and ibuprofen, which seems to carry a higher risk of anaphylactic reactions than other groups.[66] As described by others, we found that quinolones (7.8%) are the third most frequent drug associated with DHRs.[67,68]

The diagnosis of DHRs in our study was primarily based on the clinical history of the reaction, and in 22.6% of aDHR cases, the

clinician performed an SPT for confirmation. Gomes et al also reported the same figures in 2004. They recounted that 22.7% of Portuguese patients underwent skin testing.[31] In Lebanon, the health care system is funded through a combination of public, private, and personal sources, leading to a diverse financing structure.[69,70] However, it is crucial to highlight that neither public sectors nor private insurances cover the expenses of allergy skin tests in the country. As a result, these tests are exclusively available in private clinics, and patients must make out-of-pocket payments to access them. As a consequence, this might explain the lack of SPT, with only 22.6% of patients receiving the prescribed test for confirmation. In addition to the economic constraint, these results partially confirmed what is known about Middle eastern patients' hesitation toward drug allergy testing.[33]

We evaluated the trends of BLs, NSAIDs, and other antibiotic aDHR cases recorded during the 10 years. At first, we expected a decrease in cases during 2020 and 2021 since most allergy consultations worldwide were postponed due to the coronavirus disease 2019 (COVID-19) pandemic.[71,72] In addition, the nuclear-like Beirut port explosion on August 4, 2020, destroyed vital health infrastructure and left more than half of Beirut's medical facilities nonfunctional, according to the World Health Organization.[73] However, the allergy clinic's diagnostic and treatment activities were not affected. Patients were handled and followed up virtually, and severe cases were granted face-to-face consultations. Another explanation for the rise in the number of cases is the significant increase in DHRs over the last few years,[74] which can be due to the perturbation of the human microbiome by environmental impact.[75,76] This increase in DHRs diagnosed in the clinic coincides with the messenger ribonucleic acid (mRNA) COVID-19 vaccination. We believe that patients were concerned by a putative allergic reaction to the COVID-19 vaccine, which might have led them to evaluate their history of DHRs in the clinic before their first vaccine dose.[77-80]

Our study identified and analyzed 6 SJS cases (0.8%). Other studies on hospitalized patients recorded more cases, with a percentage of around 2%.[32] These disparities can be explained by the severity of the reaction and the need for hospitalization of these patients, thus not recorded in our data. All patients who suffered from SJS were elderly, with a mean age of 67 years. SJS reactions are known to occur in patients of all ages, but the highest incidence is recorded in adults older than 40.[81] Concerning the molecules causing SJS, we recorded cases of TMP/SMX, allopurinol, and metronidazole, as described by others.[82-84]

Perioperative DHRs constitute the first-line challenge for anesthesiologists and allergists.[85]

In 2014, we published the initial retrospective study examining patient profiles of individuals suffering from allergy to anesthetics. In that study, we evaluated the profiles of 17 patients having positive SPT to general anesthetics, and these findings were comparable to the outcomes of our current research.[86] Our current study population recorded 90 cases of DHRs to drugs for ambulatory use and concomitant positive SPT to molecules provided in the perioperative setting. We found opioids and NMBAs to be the 2 most common therapeutic classes involved. It is known that DHRs to NMBAs represent the leading cause of perioperative anaphylactic reactions (about 58% of cases in France).[87-89] However, the percentage of cases reported for opioids is higher than what is typically described.[90-92] In our study, the majority of SPT positive results were detected with morphine and pethidine, both of which have potent histamine-releasing properties caused by direct degranulation of mast cells.[93] NMBAs are classified as depolarizing (suxamethonium) or nondepolarizing (rocuronium, atracurium, cisatracurium).[94,95] It was previously known that suxamethonium was the most commonly found molecule, yet, its usage is decreasing.[96] Recent data suggests a rising incidence of DHRs to atracurium, rocuronium, and cisatracurium (a stereoisomer of atracurium),[87,97] which coincides with our findings. Furthermore, we evaluated the cross-reactivity between molecules of the same therapeutic class. The sensitivity and specificity of SPTs for NMBAs are estimated at 94 to 97% and 96 to 98%, respectively.[98,99] Therefore, SPTs are useful for diagnosing and evaluating cross-reactivities.[98,99] Our SPT results established that rocuronium and cisatracurium were the most commonly cross-reactive. Even though rocuronium has been frequently reported to be implicated in cross-reactivity (more than 90% of cases),[100] current reports showed disparities in cross-reactivity patterns between different geographical regions.[101] This might result from the selection bias due to varying rates of NMBA usage, assuming the NMBAs are the sensitizers.[91,100-102]

The most common opioid association we recorded was morphine and pethidine (also known as meperidine). Based exclusively on chemical structures, natural (morphine, codeine) and semisynthetic opioids (oxycodone) are structurally very similar, and possible cross-reactivity is to be evaluated. Nevertheless, synthetic opioids such as pethidine are structurally different, which suggests no cross-reactivity.[103] However, structural similarities between morphine and synthetic opioids are often overlooked. In fact, these 2 molecules share a phenylpiperidine structure and a phenylpropanolamine group,[93] which might explain the cross-reactivity observed.

In conclusion, this is the first study evaluating the clinical characteristics of all reported DHRs in Lebanon between 2012 and 2022 in an allergist outpatient clinic. Our retrospective study constitutes the first step toward a more comprehensive knowledge of the reality of DHRs in this region. More outpatient data collection and hospital-based studies must be conducted; further, biological evaluation such as basophil activation testing and a national data-based registry for DHRs must be implemented in Lebanon.

DISCLOSURE STATEMENT

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