

Multinational experience with hypersensitivity drug reactions in Latin America



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ABSTRACT

Background: Epidemiologic drug allergy data from Latin America are scarce, and there are no studies on specific procedures focusing on this topic in Latin America.

Objective: To assess the clinical characteristics and management of hypersensitivity drug reactions in different Latin American countries.

Methods: An European Network of Drug Allergy questionnaire survey was implemented in 22 allergy units in 11 Latin American countries to report on consecutive patients who presented with a suspected hypersensitivity drug reaction. Each unit used its own protocols to investigate patients.

Results: Included were 868 hypersensitivity drug reactions in 862 patients (71% of adults and elderly patients were women and 51% of children were girls, $P = .0001$). Children presented with less severe reactions than adults and elderly patients ($P < .0001$). Urticaria and angioedema accounted for the most frequent clinical presentations (71%), whereas anaphylaxis was present in 27.3% of cases. There were no deaths reported. Nonsteroidal anti-inflammatory drugs (52.3%), β -lactam antibiotics (13.8%), and other antibiotics (10.1%) were the drugs used most frequently. Skin prick tests (16.7%) and provocation tests (34.2%) were the study procedures most commonly used. A large proportion of patients were treated in the emergency department (62%) with antihistamines (68%) and/or corticosteroids (53%). Only 22.8% of patients presenting with anaphylaxis received epinephrine.

Conclusion: Nonsteroidal anti-inflammatory drugs and antibiotics were the drugs used in at least 75% of patients. More than half the reactions were treated in the emergency department, whereas epinephrine was administered in fewer than 25% of patients with anaphylaxis. Dissemination of guidelines for anaphylaxis among primary and emergency department physicians should be encouraged.

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Introduction

Hypersensitivity drug reactions (HDRs) are responsible for significant morbidity, mortality, and socioeconomic costs that are often underestimated. The true incidence of drug allergy is not known.

Most currently available epidemiologic studies have described adverse drug reactions (ADRs) rather than drug allergy specifically.¹ There are marked differences in disease prevalence, access to medicines, drug use patterns, and drug management systems between developed and developing countries, and such differences affect collecting accurate data on the frequency and nature of ADRs.

Most studies addressing drug allergy have relied on the clinical features of the reaction and the patient's history of the temporal relation between drug use and symptom onset for the diagnosis of drug allergy, with only few studies using standardized clinical questionnaires.^{1,2} Epidemiologic drug allergy data in Latin America are scarce, and there are no studies on procedures addressing the evaluation and management of drug reactions in Latin American allergy units.

The aim of this study was to describe the drugs most commonly implicated in HDRs, the presenting clinical characteristics, and the specific management approaches for the diagnosis of suspected HDRs in representative allergy units throughout Latin America.

Methods

A descriptive cross-sectional study using the European Network of Drug Allergy questionnaire² was implemented in 22 allergy units in 11 Latin American countries (Argentina, Brazil, Chile, Cuba, Colombia, Dominican Republic, Ecuador, Mexico, Paraguay, Uruguay, and Venezuela). HDRs reported in the previous 12 months before the visit by consecutive patients presenting to these allergy units were included in this analysis. If a patient had several HDRs to the same or different drugs, the last episode was reported. If more than 1 drug was involved in the reaction, a maximum of 3 were reported. If a patient presented with a new reaction to a different drug after the first report, the second episode was reported as a new case. Standard-of-care management was provided by each allergist using algorithmic protocols from that allergist's center to assess the history and needs of each patient.

Each respondent was instructed to complete the electronic questionnaire, which was available online to registered physicians. The database was accessible only to the principal researchers. Fields completed included demographic data, suspected drugs, clinical manifestations, comorbid conditions, diagnostic tests used, and management of reactions.

The study was conducted over a 2-year period, from December 2011 through November 2013. Causal relation of the reaction to the drug was categorized as certain, probable, possible, unlikely, and conditional, adapted from the World Health Organization–Uppsala Monitoring Centre Causality Categories and the Argentinean Food and Drug National Agency.^{3,4} Drugs were grouped according to an adaptation of the Anatomical Therapeutic Chemical classification of the World Health Organization Collaborating Centre for Drug Statistics Methodology.⁵ Severity of the HDR was determined according to an adaptation of the classification system of Hartwig et al⁶ and Betancourt et al.⁷ Mild reactions were considered self-limiting because they resolved over time without treatment and did not extend the patient's hospital stay. Moderate ADRs were defined as those that required therapeutic intervention and/or prolongation of hospital stay by 1 day but resolved within 24 hours owing to a change in drug therapy or the administration of a specific treatment to prevent further adverse outcomes. Severe ADRs were considered life-threatening to the patient, caused disability, led to prolonged hospital stays, required intensive medical care, or led to death. Anaphylaxis was defined as a moderate or severe reaction occurring less than 24 hours after drug administration associated with urticaria and/or angioedema (U/A), and/or respiratory (cough, dysphonia, dyspnea, wheezing/bronchospasm, rhinitis, rhinorrhea, sneezing, nasal obstruction) and/or gastrointestinal (nausea/ emesis, diarrhea, gastrointestinal cramps; R-GI), and/or

cardiovascular (CV; tachycardia, hypotension, collapse, arrhythmia) symptoms.^{8–11}

A causal relation was established based on the clinical history and allergy workup, including skin prick and intradermal tests, provocation tests, and laboratory tests, when indicated, according to the presentation of the patient and the procedures available at each center. Mechanisms of reactions were defined based on clinical presentation and time from drug intake to reaction.

Patient Characteristics

Male and female patients were categorized into 3 age groups: children and teenagers (<18 years old), adults (18 to 59 years old), and the elderly (>60 years old).

Ethical Considerations

This study encouraged researchers to adhere to a naturalistic approach, in which normal clinical practice conditions were maintained at all times. No additional interventions were performed on the patients other than those deemed appropriate by the researcher for the study and management of the HDR in question.

All information relevant to the patients was de-identified. Furthermore, all clinical information was reported anonymously and was independently linked to a code (the patient number) known only to the researcher responsible for the patient.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Facultad de Medicina y Hospital Universitario of the Universidad Autónoma de Nuevo León. The use of informed consent was exempted owing to the low risk of the study (International Regulation 45 CRF 46.117 C and article 23 of the General Health Law and Research of Mexico).

Statistical Analysis

OpenEpi software was used.¹² Non-normally distributed quantitative variables were compared using the Mann-Whitney test and qualitative variables were compared using the χ^2 test. All reported *P* values were based on 2-tailed tests; values less than .05 were considered statistically significant.

Results

Included in this analysis were 868 HDRs in 862 patients. Patients had a mean age of 36.6 years (0.3–93 years); 20.6% were children and teenagers (Table 1). Female sex was predominant across the entire study sample (67.2%), including adult and elderly populations (71.6%), whereas there was no sex predilection observed in the group of children and teenagers (adults and/or elderly vs children, *P* < .0001).

A patient-reported history of atopy was inversely related to the patient's age (adults vs children, *P* < .0001; elderly vs adults, *P* = .004). There was no significant difference in severity of HDR between allergic and nonallergic patients. A history of a drug reaction was present in 31% and a family history of allergy was present in 30.5% of patients.

Interestingly, only 52.4% of HDR cases had received the suspected drug previously, whereas 12.1% of cases presented with a history of an HDR to the inciting drug on at least 1 previous occasion.

Reactions were mild (36.1%), moderate (44%), and severe (19.9%) according to the prespecified classification of HDR severity. Severe reactions were less frequent in children (9.4%) than in adults (22.1%) and the elderly (25.2%; children vs adults or the elderly, *P* < .0001; Table 2). There was no significant difference in severity between male and female patients for severe HDRs (data not shown).

Table 1
Characteristics of study subjects

	Overall	Children (0–17 y)	Adults (18–59 y)	Elderly (60–93 y)	P value		
					Adults vs children	Elderly vs children	Elderly vs adults
Patients, n	862	178	550	134			
Age (y), mean	36.6	8.6	37.6	69.3			
Sex, n (%)							
Male	283 (32.8)	87 (48.9)	156 (28.4)	40 (29.9)	<.0001	<.0001	.73 (NS)
Female	579 (67.2)	91 (51.1)	394 (71.6)	94 (70.1)			
Atopy, n (%)	411 (47.7)	115 (64.6)	252 (45.8)	43 (32.1)	<.0001	<.0001	.004
Rhinitis, n (%)	340 (39.4)	104 (58.4)	203 (36.9)	33 (24.6)	<.0001	<.0001	.006
Asthma, n (%)	135 (15.7)	46 (25.8)	69 (12.5)	20 (14.9)	<.0001	.019	.46 (NS)
Food allergy, n (%)	40 (4.6)	29 (16.3)	26 (4.7)	3 (2.2)	<.0001	<.0001	.20 (NS)
Atopic dermatitis, n (%)	30 (3.5)	15 (8.4)	10 (1.8)	5 (3.7)	<.0001	.10 (NS)	.20 (NS)
Hymenoptera venom allergy, n (%)	10 (1.2)	1 (0.5)	9 (1.6)	0 (0)	.31 (NS)		
Previous drug reactions, n (%)	267 (31)	60 (33.7)	167 (30.4)	40 (29.8)	.40 (NS)	.47 (NS)	.91 (NS)
Family history of allergy, n (%)	263 (30.5)	78 (43.8)	162 (29.5)	23 (17.2)	<.0001	<.0001	<.01

Abbreviation: NS, not significant.

Reactions to the causative agent occurred within the first hour after receiving the agent in 46.5% of cases, whereas 32% of HDRs occurred after 1 to 24 hours and 21.5% occurred after 24 hours.

Clinical Presentation

Clinical characteristics of patients presenting with HDR are presented in Table 3. U/A was the most frequent clinical presentation (69.9%). There was no statistically significant difference among the groups studied regarding the frequency of angioedema, urticaria, or other severe dermatologic complications such as Stevens-Johnson syndrome, toxic epidermal necrolysis syndrome, and erythema multiforme.

The U/A and CV symptoms were more frequent in elderly patients (21.5%) than in adults (11.8%) and children (7.2%; $P < .01$ and $P < .001$, respectively). Anaphylaxis was present in 237 cases (27.3%). Moderate and severe reactions were present in 92.2% of patients with U/A and R-GI, 90.6% of patients with U/A and CV, and 92.9% of patients with U/A, R-GI, and CV; 95% of reactions in these groups occurred less than 24 hours after drug administration.

Body surface involvement from the HDR was less than 20% in 42.1% of cases, 21% to 50% in 28.8% of cases, and greater than 51% in 29.1% of cases.

Implicated Drugs

Certain and probable causal relation was attributed to drug groups as listed in Table 4. A single drug was involved in 712 cases, 2 drugs in 131 cases, and 3 drugs in 45 cases. The most frequently reported HDRs were to nonsteroidal anti-inflammatory drugs (NSAIDs) in 52.3% of cases. Reactions to NSAIDs occurred more frequently in children and adults than in elderly patients ($P < .001$). Beta-lactam HDRs occurred in 13.8% of all cases. Reactions to β -lactams occurred more commonly in children (20.5%) than in adults (12.3%; $P < .05$) and the elderly (10.7%; $P < .05$). Non- β -lactam antibiotic HDRs occurred in 10.1% of all cases. These reactions were more common in the elderly than in adults and children

($P < .05$ to $.0001$). Angiotensin-converting enzyme inhibitors were reported in 1% of all angioedema reactions.

Mechanism of HDR

Nonimmune hypersensitivity was the most frequent type of reaction reported for NSAID cases (69.3%). For β -lactams reactions, IgE-mediated allergic responses were the most widely attributed mechanism (55.7%), whereas for non- β -lactam antibiotics there was no reported significant difference between specific IgE-mediated (43.4%) and cell-mediated (37%) reactions. For anticonvulsant-induced reactions, cell-mediated mechanisms were considered the predominant mechanism of action (61%; Table 5).

A certain and probable causal relation between drug and reaction was present in 594 of 715 adult HDR cases (83.1%), in 149 of 176 elderly HDR cases (84.7%), and in 151 of 243 pediatric HDR cases (62.1%). The difference in causal relation for adults and/or the elderly compared with children was statistically significant ($P < .0001$).

Unrelated and uncertain drug reactions were attributed to β -lactams in 19% of adults, 6.5% of the elderly, and 58.6% of children ($P < .0001$).

Diagnostic Testing Performed

Skin prick tests (SPTs; $n = 189$) were performed in 145 cases (16.7%), yielding positive results in 56 cases (29.6% of tests). Beta-lactams (major and minor determinants, penicillin G, ampicillin, amoxicillin, and cephalosporin, varying among centers) accounted for 42.3% of tests; NSAIDs for 15.3%; non- β -lactam antibiotics for 11.1%; local anesthetics for 6.9%; corticosteroids for 4.8%; vitamins for 3.7%; neurologic drugs for 2.6%; muscle relaxants for 3.2%; and general anesthetics for 1.6% (Fig 1).

Beta-lactams HDR was suspected in 171 patients. SPTs (80) were performed in 49 of these patients, and 17 reactions were positive (10%).

Intracutaneous reactions ($n = 121$) were performed in 91 cases (10.5%), with a positive rate of 40.5%. One hundred forty-four

Table 2
Relation among age, allergy history, and severity

Severity	Children	Adults	Elderly	P value			Allergy history	No allergy history	P value, allergy vs no allergy
				Children vs adults	Children vs elderly	Adults vs elderly			
Mild, n (%)	80 (44.2)	193 (35)	40 (29.6)	<.05	<.01	.25 (NS)	160 (39)	151 (33.5)	NS
Moderate, n (%)	84 (46.4)	237 (42.9)	61 (45.2)	.34 (NS)	.77 (NS)	.61 (NS)	179 (43.7)	200 (44.3)	NS
Severe, n (%)	17 (9.4)	122 (22.1)	34 (25.2)	<.0001	<.0001	.43 (NS)	71 (17.3)	100 (22.2)	NS

Abbreviation: NS, not significant.

Table 3
Age and clinical picture

Clinical picture	All, n (%)	Children, n (%)	Adults, n (%)	Elderly, n (%)	P value		
					Children vs adults	Children vs elderly	Adults vs elderly
Angioedema	404 (46.5)	80 (44.2)	266 (48.2)	58 (43)	.43 (NS)	.77 (NS)	.29 (NS)
Urticaria	392 (45.2)	79 (43.6)	256 (46.4)	57 (42.2)	.62 (NS)	.75 (NS)	.41 (NS)
MPE, ME, and/or E exanthema	185 (21.3)	45 (24.9)	140 (25.4)	36 (26.7)	.97 (NS)	.75 (NS)	.73 (NS)
Erythema multiforme, SJS, and TENS	29 (3.3)	5 (2.8)	21 (3.8)	3 (2.2)	.55 (NS)	.78 (NS)	.39 (NS)
Angioedema without urticaria	221 (25.5)	50 (27.6)	141 (25.5)	30 (22.2)	.52 (NS)	.26 (NS)	.44 (NS)
Urticaria without angioedema	207 (23.8)	49 (27.1)	130 (23.6)	28 (20.7)	.30 (NS)	.18 (NS)	.51 (NS)
U/A	607 (69.9)	129 (69.9)	392 (71)	86 (63.7)	.76 (NS)	.12 (NS)	.11 (NS)
U/A + R-GI symptoms	232 (26.7)	53 (29.3)	174 (31.5)	43 (31.6)	.65 (NS)	.66 (NS)	.91 (NS)
U/A + CV symptoms	107 (12.3)	13 (7.2)	65 (11.8)	29 (21.5)	.09 (NS)	<.001	<.01
U/A + CV + R-GI	84 (9.7)	10 (5.5)	49 (8.9)	25 (18.5)	.16 (NS)	<.001	<.01
Anaphylaxis	237 (27.3)	43 (23.8)	157 (28.4)	37 (27.4)	.26 (NS)	.49 (NS)	.84 (NS)

Abbreviations: CV, cardiovascular (tachycardia, hypotension, collapse, arrhythmia); E, eczematoid; ME, macular exanthema; MPE, maculopapular exanthema; NS, not significant; R-GI, respiratory (cough, dysphonia, dyspnea, wheezing/bronchospasm, rhinitis, rhinorrhea, sneezing, nasal obstruction) and/or gastrointestinal (nausea/emesis, diarrhea, gastrointestinal cramps); SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis syndrome; U/A, urticaria and/or angioedema.

serologic specific IgE tests were performed in 71 cases (8.2%), with a positive rate of 19.4%. Beta-lactams were the most frequently ordered specific IgE test (94.4%). Basophil histamine release was performed in 23 cases (2.6%), basophil activation test in 7 cases (0.8%), and lymphocyte transformation test in 1 case. Provocation tests (n = 410) were performed in 304 cases (35%). NSAIDs (57.1%) and β -lactams (14.9%) were the most frequently challenged drugs, followed by non- β -lactam antibiotics (5.9%), local anesthetics (3.2%), and vitamins (2.2%). Provocation test reactions were positive in 30.2% of cases (Fig 2).

Treatment

Sixty-two percent of reactions were treated in the emergency department (ED), 21% by an allergist, 5.8% by a general practitioner, 5.4% were self-medicated, and 5.5% received no medication. Corticosteroids and antihistamines were the most frequently administered drugs (47.1%; Table 6).

Only 22.8% of the 237 anaphylactic reactions included were treated acutely with epinephrine. Interestingly, when there was CV involvement, this rate increased to 40.9%.

Discussion

Hyperreactive drug reactions are common reasons for patient referral to allergy departments. They are the third most common cause of consultation after allergic rhinitis and asthma in Spain¹³ and the sixth most common reported in San Antonio, Texas.¹⁴ To the authors' knowledge, this is the first attempt to provide a description of the HDR causative agents, the clinical presentation,

diagnostic studies performed, and HDR treatment across the spectrum of Latin American countries.

The present study has confirmed, similar to other studies, that in adults and the elderly, women are more likely to develop drug allergies than men, whereas no sex predilection in children was observed.^{15–19} Other researchers have reported similar findings in some specific situations such as perioperative anaphylaxis.²⁰ The similar incidence in sex for HDR before adolescence suggests a possible role for sex hormones related to the increase of HDRs observed in women. Sex differences also have been reported regarding differences in patterns of drug consumption or genetic predisposition resulting in an HDR.²¹

No significant difference in HDR severity in patients with vs without an allergic history was observed. Banerji et al,²² in a retrospective analysis of 716 patients with a visit to an ED and/or hospitalization for drug-induced anaphylaxis, found that patients with asthma, allergic rhinitis, and eczema did not differ in the severity of the event, site of treatment (discharged from ED vs hospital admission), or management while in the ED or hospital compared with patients without any concomitant allergic conditions. The presumption that atopic predisposition contributes to a more severe allergic reaction to drugs, as stated in many publications,^{23,24} requires further investigation to better understand host risk factors for drug hypersensitivity.

Urticaria and/or angioedema were the most frequent clinical presentations (69.9%) followed by exanthema, similar to previous reports.^{13,25} In 27.3% of cases, moderate or severe U/A and R-GI or CV involvement occurred some minutes to a few hours after drug administration, fulfilling the criteria for a diagnosis of anaphylaxis.^{8–11}

Table 4
Drug groups: certain and probable reactions

Drug group	All, n (%)	Children, n (%)	Adults, n (%)	Elderly, n (%)	P value		
					Children vs adults	Children vs elderly	Adults vs elderly
NSAIDs	454 (52.3)	87 (58)	313 (51.5)	54 (36.2)	.28 (NS)	<.001	<.001
β -Lactams	120 (13.8)	31 (20.5)	73 (12)	16 (10.7)	<.05	<.005	.62 (NS)
Non- β -lactam antibiotics ^a	88 (10.1)	6 (4)	55 (9.2)	27 (18.1)	<.05	<.0001	<.01
Anticonvulsants	27 (3.1)	2 (1.3)	19 (3.1)	6 (4)	.22 (NS)	.17 (NS)	.6 (NS)
Other neurologic drugs	10 (1.2)	0	7 (1.2)	3 (2)			.44 (NS)
Local anesthetics	15 (1.7)	0	10 (1.6)	5 (3.4)			.22 (NS)
Contrasts	11 (1.3)	0	8 (1.3)	3 (2)			.54 (NS)
ACE inhibitors	12 (1.4)	0	4 (0.7)	8 (5.4)			<.001
Other cardiologic drugs	13 (1.5)	0	3 (0.5)	10 (6.7)			<.0001
Steroids	13 (1.5)	2 (1.3)	5 (0.8)	6 (4)	.58 (NS)	.17 (NS)	<.05
Vitamins	16 (1.8)	1 (0.6)	13 (2.1)	2 (1.3)	.23 (NS)	.62 (NS)	.56 (NS)

Abbreviations: ACE, angiotensin-converting enzyme; NS, not significant; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aMain non- β -lactams in order of frequency: ciprofloxacin, TMP-SMX (trimethoprim-sulfamethoxazole), and levofloxacin.

Table 5
Mechanisms of reactions

Type of reaction	All, n (%)	NSAIDs, n (%)	BLA, n (%)	N-BLA, n (%)	Anticonvulsants, n (%)
Type I reaction (IgE mediated)	404 (31.8)	92 (17.8)	107 (55.7)	49 (43.4)	3 (7.3)
Type II reaction (antibody mediated)	5 (0.4)	3 (0.6)	0	0	0
Type III reaction (immune complex mediated)	12 (0.9)	0	1 (0.5)	2 (1.8)	3 (7.3)
Type IV reaction (cell mediated, late-type reaction)	233 (18.3)	32 (6.2)	57 (29.7)	37 (32.7)	25 (61)
Cytotoxic reaction (cell mediated)	7 (0.6)	0	1 (0.5)	3 (2.7)	1 (2.4)
Nonallergic hypersensitivity	492 (38.7)	359 (69.3)	13 (6.8)	12 (10.6)	8 (19.5)
Pharmacologic reaction	81 (6.4)	27 (5.2)	8 (4.2)	8 (7.1)	1 (2.4)
Psychophysiologic reaction	16 (1.3)	3 (0.6)	2 (1)	2 (1.8)	0
Other	20 (1.6)	2 (0.4)	3 (1.6)	0	0

Abbreviations: BLA, β -lactam antibiotics; N-BLA, non- β -lactam antibiotics; NSAIDs, nonsteroidal anti-inflammatory drugs.

No significant difference in the frequency of these reactions was found among children, adults, and the elderly, but children presented with less severe manifestations.

The NSAIDs were the most frequently implicated group of drugs involved with HDRs in adults, the elderly, and children. This is in contrast to some previous studies reporting that β -lactams are the drugs most frequently involved in HDRs.^{25–28} The present findings are consistent with several other studies^{19,29–32} that have reported a similar predominance of NSAIDs as causative agents of HDRs. The increased prevalence of NSAIDs is not surprising because these drugs are easily obtained over the counter in most Latin American countries. Moreover, the prevalence of self-medication in children and young adults is high in this region, and NSAIDs are the most commonly used pharmacologic agents.^{33,34} Selective NSAID HDRs, primarily manifesting with symptoms of U/A, were classified as type I reactions in this population, which accounted for almost 18% of NSAID cases. This finding is slightly lower than the 24% of selective responders described by Doña et al³⁵ in 659 patients evaluated for NSAID HDRs. Type IV or late reactions were present in 6% of the present NSAID cases; however, it was not possible to clearly differentiate selective responders from drug intolerance in this group.

Beta-lactams ranked second in frequency. These reactions were more frequent in children than in adults and the elderly ($P < .05$). The third group was comprised of non- β -lactam antibiotics, the

frequency of which was higher in the elderly than in adults and children.

Angiotensin-converting enzyme inhibitors were involved in only 1% of angioedema cases, which is consistent with what has been previously reported in the literature.^{36–39} The present findings are in contrast to those of Lin et al⁴⁰ who described an increase in hospitalization rates for angioedema in the United States during the 2000s, which was associated with angiotensin-converting enzyme inhibitors.

Beta-lactams were more frequently involved in uncertain and nonrelated reactions in children compared with adults to an even greater extent than observed for the frequency of NSAID HDRs in this group. This could be explained by the larger proportion of exanthematic reactions in children treated with β -lactams during viral infections. In children, nonpruritic maculopapular rash occurs frequently during febrile illnesses, as observed in 3% to 7% of children taking ampicillin in 1 study.⁴¹ The mechanisms of these exanthemas are not well understood. The immune response to an antibiotic could be altered by a response to the viral infection or occur secondary to complement activation and release of anaphylatoxins (C3a and C5a), resulting in an allergic-like reaction in the presence of an antibiotic, which is highly unlikely to reoccur at re-exposure.^{28,42,43}

No specific diagnostic procedure was consistently used by participating physicians to assess HDRs. Physicians mostly preferred

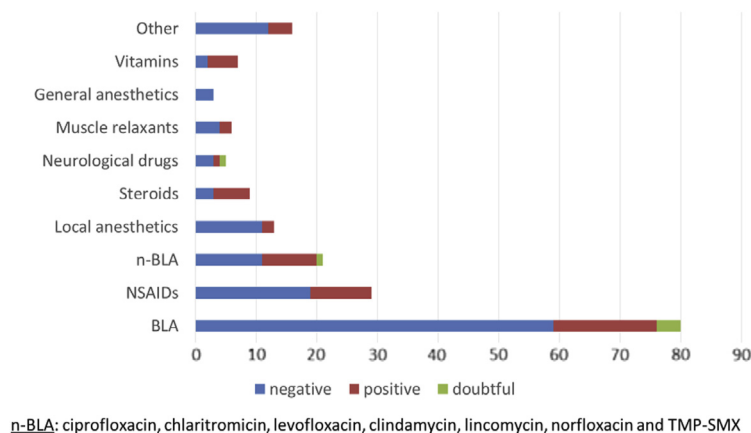


Figure 1. Skin prick test results. The β -lactams (BLAs) yielded the most common positive results (80 cases in 49 patients), followed by nonsteroidal anti-inflammatory drugs (NSAIDs), non- β -lactams (n-BLAs), and local anesthetics.

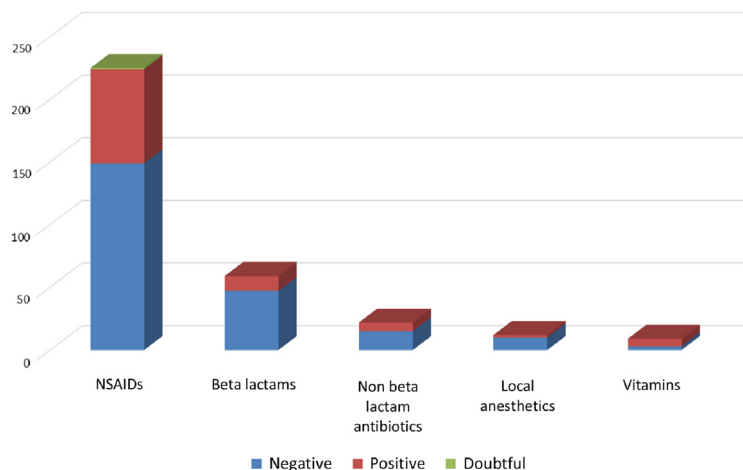


Figure 2. Results of drug provocation tests: 225 nonsteroidal anti-inflammatory drug (NSAID) and 59 β -lactams provocation tests were performed (see text).

drug provocation tests (DPTs) over other diagnostic approaches. DPTs were performed in 35% of cases (mainly to NSAIDs), 30% of which showed positive reactions. The small percentage of positive provocation test reactions might be related to the fact that most DPTs were performed with a different drug from those involved in the HDR to offer a therapeutic option for the patient. In Brazil, Aun et al,⁴⁴ in a retrospective analysis of 500 ADRs, found that 39% of DPTs performed resulted in only 4.1% positive reactions and, as in the present study, they primarily used drugs that would be alternatives to the drug that had supposedly caused the reaction. Messaad et al²⁹ showed that of 1,372 DPTs, only 241 reactions (17.6%) were positive. A study in children with suspected drug allergy found that only 23.9% had a positive DPT reaction.⁴⁵ Another recent study of DPT in children with probable NSAID hypersensitivity found 14% and 44% positivity to single and multiple NSAID reactors, respectively.⁴⁶ A World Allergy Organization survey⁴⁷ found that in Latin America SPTs were the second most common procedure used to assess HDRs. The present data confirm these estimations from national and regional associations. SPTs, mainly to β -lactams, were used in 16.7% of cases, of which almost 30% were positive. Although this figure seems somewhat high, it represents only 10% of patients with suspected β -lactam HDR and is consistent with the findings of Raja et al.⁴⁸ In contrast with most European and American studies,^{13,29} in vitro tests were used infrequently by the participating centers. Specific IgE to β -lactams was the most commonly used in vitro test (<10% of cases). Cellular tests, such as the basophil activation test or lymphocyte transformation test, were almost never used, likely because of their low availability in Latin America and cost.

In contrast with current anaphylaxis recommendations,^{8–11} epinephrine was used in fewer than 25% of anaphylactic reactions and in 40% of cases when there was CV involvement. Nevertheless, no mortality was reported. Klemans et al,⁴⁹ in the Netherlands, found that only 27% of patients with food anaphylaxis and

respiratory symptoms treated by general practitioners received epinephrine. This rate increased to 73% when there was CV involvement. In the study by Banerji et al,²² only 8% of patients with drug-induced anaphylaxis treated in the ED received epinephrine. Droste and Narayan⁵⁰ found that hospital physicians were not knowledgeable regarding current recommendations for anaphylaxis. Because most of these reactions were treated in EDs, dissemination of anaphylaxis guidelines in this group of physicians should be encouraged.

The strengths of this study are the use of a validated standardized clinical questionnaire² plus the specific procedures of each participating center to confirm the diagnosis of HDRs. In addition, the limited time frame from the drug reaction to its reporting (1 year) minimized the potential for data loss or miscommunication.

Limitations of this study include the potential for population bias and treatment and reporting differences among sites. Therefore, the present findings may not be truly generalizable because they may not reflect the incidence or prevalence of HDRs across all medical communities in Latin America. Furthermore, there was no comparative control group used in this analysis. It is also likely that only the most severe and/or complex cases were referred to an allergy clinic. In the study by Banerji et al,²² only 14% of patients received any subsequent care with an allergist or immunologist within 1 year after the initial ED visit and/or hospitalization for drug-induced anaphylaxis. These investigators also found that patients with a concomitant allergic condition were more likely to see an allergist or immunologist than those without a concomitant allergic condition. The authors selected the participating facilities based on their experience in research and their ability to comply with the protocol, so the results might not reflect less knowledgeable medical facilities across Latin America.

In summary, this study describes the main features of HDRs in Latin America by providing a description of the studies and treatment performed using a validated and standardized questionnaire.² The results of this study indicate the need to improve dissemination and implementation of guidelines and education of the general population about the public health issue of HDRs and the dangers of self-medication.

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Table 6

Drug treatment

Severity	AH, n (%)	Steroids, n (%)	AH and steroids, n (%)	Epinephrine, n (%)
Mild	217 (25)	113 (13)	94 (10.8)	2 (0.2)
Moderate	285 (32.8)	231 (26.6)	189 (21.8)	11 (1.3)
Severe	142 (16.4)	138 (15.9)	126 (14.5)	61 (7)
All	644 (74.2)	482 (55.5)	409 (47.1)	74 (8.5)

Abbreviation: AH, antihistamines.

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Appendix

Latin America Drug Allergy Interest Group

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