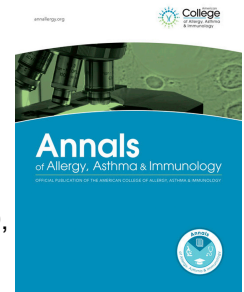


Accepted Manuscript

Drug Hypersensitivity Reactions in the Americas: Similarities and Differences

Pedro Giavina-Bianchi, MD, PhD, Edgardo Jares, MD, Marcelo Vivolo Aun, MD, PhD, Bernard Thong, MD



PII: S1081-1206(19)30099-7

DOI: <https://doi.org/10.1016/j.anai.2019.02.007>

Reference: ANAI 2815

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 8 February 2019

Accepted Date: 8 February 2019

Please cite this article as: Giavina-Bianchi P, Jares E, Aun MV, Thong B, Drug Hypersensitivity Reactions in the Americas: Similarities and Differences, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.02.007>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Drug Hypersensitivity Reactions in the Americas: Similarities and Differences**Pedro Giavina-Bianchi, MD, PhD ^a****Edgardo Jares, MD ^b****Marcelo Vivolo Aun, MD, PhD ^{a,c}****Bernard Thong, MD ^d****Affiliations**

^a Clinical Immunology and Allergy Division, University of Sao Paulo, Sao Paulo, BR. Electronic address: pbianchi@usp.br

^b Libra Foundation, Buenos Aires, Argentina. Electronic address: edgardo.jares@gmail.com

^c Faculdade Israelita de Ciências da Saúde Albert Einstein (FICSAE) School of Medicine. Electronic address: marcelovivoloaun@gmail.com

^d Tan Tock Seng Hospital, Singapore, Singapore. Electronic address: bernard_thong@ttsh.com.sg

Word Count: 2158**References:** 41**Statement of contribution**

All authors meet the three conditions:

- 1) Substantial contributions to conception of the correspondence.
- 2) Drafting the article and revising it critically for important intellectual content.
- 3) Final approval of the version to be published.

No Financial Support

Statement of conflicts of interest

I confirm that this paper has been read and approved by all the co-authors, and that no conflicts of interest exist regarding its publication.

Author for correspondence:

Pedro Giavina-Bianchi

R. Prof. Artur Ramos 178 ap.211A

Jd. América, São Paulo, SP, Brazil

CEP:01454-904

Telephone and FAX number: 55 11 30713189

Email: pbianchi@usp.br

Abbreviations:

HRs	hypersensitivity reactions
ADRs	adverse drug reactions
SCARs	serious cutaneous adverse drug reactions
NSAIDs	non-steroidal anti-inflammatory drugs
EHR	electronic health record
LA	Latin America
DPTs	drug provocation tests
DIA	drug induced anaphylaxis
BAT	basophil activation test
SJS	Stevens Johnson syndrome
TEN	toxic epidermal necrolysis
DIHS	drug induced hypersensitivity syndrome

Key words:

Drug allergy

Epidemiology

Hypersensitivity Reactions

Anaphylaxis

Immunologically-mediated

Management

Drugs are the most frequent cause of fatal anaphylaxis worldwide(1). The prevalence of adverse drug reactions (ADRs), including allergy, is known to be related to drug exposure frequency, gender, age, ethnicity and genetic factors, and it varies according to the classes of drugs, definitions of hypersensitivity reactions (HRs) and study design. Drug usage patterns vary significantly with time and geography, both across large countries and around the world(1-3).

Immediate HRs (IHRs) occur within 1-6h after drug exposure, involve mast cell/basophil degranulation and are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm and anaphylaxis. IHRs may be allergic, generally mediated by a IgE specific immune response, or non-allergic, with direct mast cell/basophil activation(2). Only a small fraction of reported drug “allergy” can be confirmed to be immunologically-mediated drug hypersensitivity. In the allergy/immunology practice, two of the commonest HRs are urticarial/angioedema induced/exacerbated by NSAIDs, almost always non-allergic HRs, and exanthemas/rashes induced by amoxicillin, many of them being allergic reactions.

Incidence and mortality due to ADRs in hospitalized patients are 10-20% and 0.32%, respectively(4-5). A recent Brazilian study actively assessing 472 in-patients observed 16.2% of ADRs, 3.2% of HRs and an increase of 10% in the rate of ADR for each additional administered drug. The medication groups most frequent involved in ADRs were antibiotics (21.2%), opioids (13.8%) and iodinated contrast media (10.6%). Non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly prescribed drugs and the fourth cause of ADRs(5).

In the United States, penicillins were the most commonly prescribed class of antibiotics in 2014, and amoxicillin and amoxicillin/clavulanic acid account for 91.6% of all penicillins dispensed. Total antibiotic prescriptions varied from 615 per 1000 individuals per year in the western United States to over 1,021 per 1000 individuals per year in some southern states(6).

In 2010, the three leading causes of fatal anaphylactic reactions in the United States were antibiotics, diagnostic agents, and anticancer drugs(7). The most commonly reported drug allergy around the world is still penicillin. Around 10% of the general population refer to be “penicillin allergic”. However, less than 5% of unselected individuals with the “penicillin allergy” label can have the diagnosis confirmed with the reference standard test, an oral amoxicillin challenge. Most patients have been mistakenly diagnosed as penicillin allergic, but others have lost drug-specific IgE and became non-reactors. These non-allergic reactions include side-effects such as headaches, vasovagal reactions, other benign reactions or associations, fear because of family history, or other unknown causes(8).

The overdiagnosis of penicillin allergy is harmful. The incorrect diagnosis is associated with high morbidity, treatment cost and may increase mortality. Patients label as allergic are at higher risk for prolonged length of stay in the hospital, readmissions, acquisition of multidrug-resistant organisms, *Clostridium difficile* infection, and treatment failure. Lately, several programs in USA have been developed and studies have shown the importance, feasibility and efficacy of “delabeling” patients with the mistaken diagnosis of penicillin allergy(9).

In Latin America (LA), beta lactams are also the most frequent inducers of allergic HRs, including allergic anaphylaxis, in particular in children and adolescents. In this group, however, uncertain and unrelated reactions were more frequent than in adults and elderly patients. This could be explained by exanthematic reactions occurring during viral infections treated with beta lactams and would be one of the reasons of the large proportion of the population claiming to be “allergic” to beta lactams(10,11). Immediate-reading skin tests are good biomarkers, and it is crucial to perform drug provocation tests (DPTs) to confirm or discharge a presumptive diagnosis and to manage HRs to drugs properly. The lack of skin test reagents to mayor and

minor determinants in most countries of LA, as well as the difficult access to in vitro test, such as serum specific IgE and tryptase, are important obstacles to the correct diagnosis of this group of patients.

NSAIDs are the most used and prescribed medicine to outpatients and hospitalized patients worldwide. Furthermore, they are easily obtained as over-the-counter drugs and many patients do not remember to refer them when answering the question: “What medications are you taking?”.

Almost ten years ago, while USA and Europe were studying antibiotics as the main cause of anaphylaxis, we identified NSAIDs as the main cause (48.7%) of drug-induced anaphylaxis (DIA) in Brazil. Most of these patients reported blended reactions, with simultaneous cutaneous and respiratory manifestations, non-selective induced by NSAIDs. Although these non-IgE mediated anaphylaxis tend to be less severe than the allergic ones, life-threatening reactions did occur. Anaphylaxis due to NSAIDs were underdiagnosed and undertreated, since 2/3 of all patients referred previous HRs to NSAIDs, and only 1/3 were treated with epinephrine(10).

Then, another study showed a similar scenario in LA, NSAIDs being the most frequent HRs inducers in children (58%), adults (51.5%) and elderly (36.2%). Beta lactams were the second DIA inducer (14.3%). HRs to NSAIDs were classified as non-selective immediate HRs (non-allergic) in 69.3%; selective immediate HRs (IgE-mediated) in 17.8%; and T-cell-mediated HRs in 6.2% of the cases. DPT were the most frequent diagnostic tool used by the allergist, not with diagnostic purposes, but to find a safe alternative drug for the patient (provocations with weak cyclooxygenase-1 inhibitors or selective cyclooxygenase-2 inhibitors)(11).

The third most commonly reported drug HR in the United States, after penicillins and opiates, is to NSAIDs. Opiates are direct mast cell activators and immunologically-mediated

hypersensitivity is virtually never implicated in reported opiate intolerance. NSAIDs HRs is reported by 2.66% of women and 1.34% of men(6). The most common clinical scenario related to a new NSAID “allergy” report is an episode of urticarial/angioedema induced by NSAID use in a patient with or without previous history of chronic spontaneous urticaria. Much more rarely there is NSAID exacerbated respiratory disease.

Among adults, neuromuscular blocking agents administered during the perioperative period, radiocontrast media (ionic contrast more commonly than gadolinium based agents) and chemotherapeutic agents/biologics are additional causative agents with increasingly prevalence. Regarding perioperative anaphylaxis, latex is still a problem in LA, unlike in the United States and Europe(1, 10).

Beta lactam antibiotics and NSAIDs predominate as the main causes of drug induced IHRs in Americas, the former inducing more severe reactions and the latter being more prevalent (10,11) (Table 1). IHRs are underdiagnosed, as observed in reactions to NSAIDs, but may be overdiagnosed in other cases, as seen in patients mistakenly label as “penicillin allergic”(1,10). Awareness of health professionals and the rational use of medications are important to prevent and improve the management of IHRs.

1. Giavina-Bianchi P, Aun MV, Kalil J. Drug-induced anaphylaxis: is it an epidemic? *Curr Opin Allergy Clin Immunol*. 2018;18(1):59-65.
2. Zhou L, Dhopeshwarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy*. 2016;71(9):1305-13.
3. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69(4):420-37.
4. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One*. 2009;4(2):e4439.
5. Ribeiro MR, Motta AA, Marcondes-Fonseca LA, Kalil-Filho J, Giavina-Bianchi P. Increase of 10% in the Rate of Adverse Drug Reactions for Each Drug Administered in Hospitalized Patients. *Clinics (Sao Paulo)*. 2018;73:e185.
6. https://www.cdc.gov/antibiotic-use/community/pdfs/AnnualReportSummary_2014.pdf.
7. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. *J Allergy Clin Immunol*. 2014;134(6):1318-28.e7.
8. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep*. 2014;14(11):476.
9. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: Assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol*. 2017;140(1):154-61.e6.
10. Aun MV, Blanca M, Garro LS, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. *J Allergy Clin Immunol Pract*. 2014;2(4):414-20.

11. Jares EJ, Sánchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol.* 2014;113(3):282-9.
12. Ribeiro-Vaz I, Marques J, Demoly P, Polónia J, Gomes ER. Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority. *Eur J Clin Pharmacol.* 2013;69(3):673-81.
13. Ensina LF, de Lacerda AE, de Andrade DM, Machado L, Camelo-Nunes I, Solé D. Drug-induced anaphylaxis in children: nonsteroidal anti-inflammatory drugs and drug provocation test. *J Allergy Clin Immunol Pract.* 2014;2(6):825.
14. Faria E, Rodrigues-Cernadas J, Gaspar A, et al. Drug-induced anaphylaxis survey in Portuguese Allergy Departments. *J Investig Allergol Clin Immunol.* 2014;24(1):40-8.

Table 1. Main agents involved in drug-induced anaphylaxis by age

Study (year)	Main Agent Involved (%) / Sex Predominance	
	Age < 18 years	Age > 18 years
Ribeiro-Vaz et al.(12) (2013)	Vaccines and Immunoglobulins (37%)/ Male	Antibiotics (17%)/ Female
Aun et al.(10) (2014)	—	NSAIDs (48.7%)/ Female
Ensina et al.(13) (2014)	NSAIDs (61.5%)/ Male	—
Faria et al.(14) (2014)	Antibiotics (46.2%)/ Male	NSAIDs (48.4%)/ Female
Jares et al. (11) (2015)	NSAIDs (58%)/ Male	NSAIDs (51.5%)/ Female