Revisiting the Impact of Misdiagnosed Drug Hypersensitivity in Hospitalized Patients: A 10-Year Perspective

Bernaola J[1]*, Otal-Buesa M[1]*, Barroso B[1,2], Valverde-Monge M[1,2], Sastre J[1,2]

[1]*Allergy Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain*

[2]*CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain*

**Both authors contributed equally.*

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Drug hypersensitivity reactions (DHRs) have become increasingly prevalent in recent years [1,2]. However, discrepancies between medical records and the results of thorough allergology studies are frequent [3]. As previously demonstrated [4], the reliability of reported DHRs in hospitalized patients is often uncertain, leading to associated medical and economic consequences. Ten years ago, Sastre et al [4] conducted a study in a tertiary university hospital (Fundación Jiménez Díaz, Madrid, Spain) to determine the frequency with which DHRs reported by patients on admission were confirmed by an allergy work-up and to calculate the costs associated with misdiagnosis. The authors confirmed the original diagnosis of DHR in 37% of patients, with a 4-fold increase in the associated cost due to misdiagnosis, primarily involving antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).

We present the results of a study carried out in the same hospital with the same methodology to assess whether, 10 years later, there are significant differences in the frequency of misdiagnosis of DHR and the associated costs.

On a randomly chosen day, DHR data were extracted from the electronic medical records of all hospitalized patients. Patients were only included after giving their informed consent, which was approved by the Ethics Committee. It was verified whether the attending physician inquired about a personal history of drug allergies. The diagnosis of DHR was considered confirmed if the symptoms were highly suggestive or if the patient had a previous allergy study that confirmed it. In the remaining patients, skin prick tests, intradermal tests, and challenge tests were performed, as necessary, to confirm or rule out DHR after hospital discharge. The modified treatment regimen received by each patient based on the attending physician's opinion of the presence of DHR and the resulting cost were evaluated to determine deviations from standard care. Drug prices were obtained according to the Spanish Recommended Retail Price.

On the day selected, 470 patients were hospitalized. Of these, 105 (22%) were diagnosed with DHR, although only 46 (44%; mean age, 67.6 [15.2] years; 56.5% female) signed the informed consent and were finally included. A significant portion of patients (56%) did not sign the informed consent for various reasons (eg, low level of consciousness, cognitive impairment, admission to intensive care or psychiatry, and outright refusal to participate).

A total of 66 DHR labels were observed in 46 patients. Of the drugs included, 24 (36%) were antibiotics (16 ß-lactam and 8 other), 17 (26%) NSAIDs, 7 (11%) contrast media, and 18 (27%) other drugs, including heparin, tramadol, angiotensin-converting enzyme inhibitors, chlorhexidine, mycophenolate mofetil, tamsulosin, ondansetron, pethidine, lorazepam, furosemide, pregabalin, and codeine (Figure).

At admission, 76% of physicians verified the diagnosis of DHR. In 11 patients (24%), the abovementioned drugs were necessary during admission, with the result that the diagnosis of DHR led to changes in the drug administered. In 7 cases, penicillin was replaced by cephalosporins, clindamycin, levofloxacin, or vancomycin. Tramadol was replaced by fentanyl in one patient and an NSAID by tramadol in another. Iodinated contrast medium was not used in one patient despite the indication, and in a second patient, a drug challenge was performed during admission, ruling out allergy. These drug changes increased median treatment costs 4.4-fold (range, 1.5-26.1).

The allergology study was conducted in 42 (64%) of the DHR labels, revealing that in 18 (43%), the original diagnosis of DHR was correct (14 were obtained from the clinical history; 2 were confirmed by positive skin prick and intradermal test result; and 2 were corroborated by a positive drug challenge result). However, in 21 patients (50%), the original diagnosis of DHR was incorrect: 4 were nonallergic adverse events (cough due to angiotensin-converting-enzyme inhibitors, thrombocytopenia due to heparin, chemical phlebitis due to quinolones, and myalgia due to enalapril);

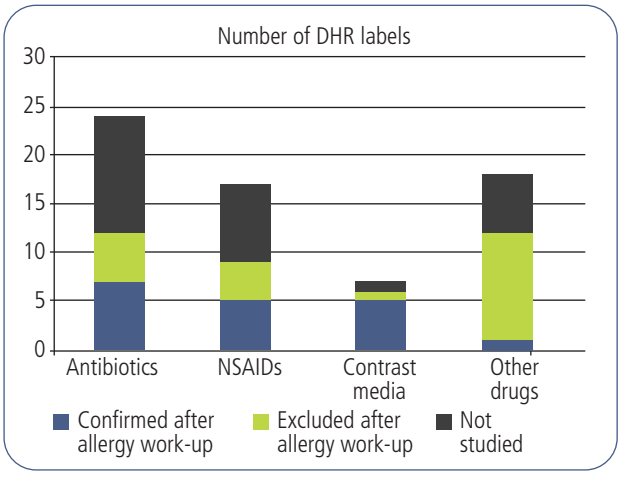

Figure. Number of drug hypersensitivity labels in hospitalized patients at the time of hospital admission (total), number of diagnoses not assessed, and number of diagnoses confirmed and excluded after an in-depth allergology study. DHR indicates drug hypersensitivity reaction; NSAID, nonsteroidal anti-inflammatory drug.

5 were ruled out by the clinical history; 2 were excluded by negative skin prick and intradermal test results; and 10 were ruled out by a negative drug challenge. Lastly, in 3 patients (7%), it was infeasible to complete the study. Of the 66 labels, 24 (36%) were not studied owing to the death of the patient, refusal to participate in the study, and nonattendance at the appointment (Figure).

Compared with the study carried out 10 years ago [4], no noticeable differences were observed in terms of the proportion of DHRs (22% vs 18%), consistent with data previously reported by Ojeda et al [1] (17.7%) and Thong et al [5] (10%-20%). Antibiotics and NSAIDs continue to be the most frequent sources of DHR. Interestingly, over the past 10 years, diagnoses have been increasingly verified by attending physicians (60% vs 76%). The economic consequences of misdiagnosis have remained significant over the decade. In this regard, Mattingly et al [6] reported lower inpatient costs for patients who did not self-report penicillin allergy, with savings ranging from $1145 to $4254 per patient [6]. King et al [7] reported overall savings of around $11 000 in 37 misdiagnosed patients, including the cost of penicillin skin test material, and Li et al [8] found a potential cost saving of between £5851.18 and £14 471.93.

The percentage of correct diagnoses we observed was slightly higher than that reported a decade ago (43% vs 37%). Nevertheless, both studies reveal that a significant portion of DHR labels remain incorrect (50% present vs 56% a decade ago).

Of note, a significant percentage of patients declined to participate in the study because of fear, distrust, or underestimation of the consequences of a drug allergy label, thus potentially indicating a selection bias.

A decade of progress has seen improvements in some areas, such as the frequency of verification of DHR labels. However, the core issue of diagnostic accuracy remains unresolved, and the economic burden of misdiagnosing DHR continues to strain health care resources.

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Conflicts of Interest

BB has received the following: payment for lectures from Roxall, Chiesi, Sanofi; payment for expert testimony from ALK; support for attending meetings from Allergy Therapeutics, Sanofi, Stallergenes-Greer, Roxall, Allergopharma, and Merck. JS reports the following: serving as a consultant for Sanofi, AbbVie, and Novartis; lecture fees from Sanofi, GSK, and Faes Farma; support for attending meetings and/or travel from Sanofi; holding unpaid leadership or fiduciary roles for boards, societies, committees, or advocacy groups in the SEAIC, AAAAI, and EAACI; and grant support for research from Sanofi. The remaining authors declare that they have no conflicts of interest.

References

1. Ojeda P, Sastre J, Olaguibel JM, Chivato T; investigators participating in the National Survey of the Spanish Society of Allergology and Clinical Immunology Alergológica 2015. Alergológica 2015: A National Survey on Allergic Diseases in the Adult Spanish Population. J Investig Allergol Clin Immunol. 2018;28(3):151-64.
2. Mayorga C, Fernandez TD, Montañez MI, Moreno E, Torres MJ. Recent developments and highlights in drug hypersensitivity. Allergy. 2019;74(12):2368-81.
3. Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin Allergy Testing Should Be Performed Routinely in Patients with Self-Reported Penicillin Allergy. J Allergy Clin Immunol Pract. 2017;5(2):333-4.
4. Sastre J, Manso L, Sanchez-García S, Fernández-Nieto M. Medical and economic impact of misdiagnosis of drug hypersensitivity in hospitalized patients. J Allergy Clin Immunol. 2012;129(2):566-7.
5. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71(5):684-700.
6. Mattingly TJ 2nd, Fulton A, Lumish RA, Williams AMC, Yoon S, Yuen M, et al. The Cost of Self-Reported Penicillin Allergy: A Systematic Review. J Allergy Clin Immunol Pract. 2018;6(5):1649-54.
7. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with ß-lactam allergies: Effect on antibiotic selection and cost. Ann Allergy Asthma Immunol. 2016;117(1):67-71.
8. Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. J Clin Pathol. 2014;67(12):1088-92.

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Jaime Bernaola Abraira
Fundación Jiménez Díaz
Avenida de los Reyes Católicos, 2
28040, Madrid
E-mail: Jaimebernaola10@gmail.com

