The impact of a drug allergy label in an internal medicine ward

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Abstract

Drug hypersensitivity reactions are presumably immune-mediated reactions that cause reproducible signs and/or symptoms. Overdiagnosis of drug allergy, frequently self-reported, is common and carries significant limitations. We intended to analyze the frequency and impact of drug allergy in hospitalized patients.

A retrospective study was conducted in an Internal Medicine ward at a tertiary hospital in Portugal. All patients with a drug allergy report admitted within a 3-year period were included. Data were collected from their electronic medical records.

We found that 15.4% of patients had a report of drug allergy, with antibiotics being the most common (56.4%), followed by non-steroidal anti-inflammatory drugs (21.7%) and radiocontrast media (7.0%). The allergy report affected the clinical approach of 14.5% of patients by motivating the use of second-line agents, or the eviction of necessary procedures. The usage of alternative antibiotics entailed a cost increase of 2.4 times. There were 14.7% of patients to whom the suspected drug was administered: 87.0% tolerated and 13.0% developed a reaction. Only 1.9% were referred to our Allergy and Clinical Immunology department and proceeded in their allergy study.

In this study, a considerable number of patients had a drug allergy label on their records. This label contributed to an increase in the cost of treatment, or the avoidance of necessary exams. However, disregarding an allergy record may lead to potentially life-threatening reactions that proper risk assessment could avoid. Further investigation should always be part of the follow-up routine of these patients, and better articulation between departments should be encouraged.

Key Words

Drug allergy; Antibiotic allergy; Self-reported allergy; Allergy cost; Allergy impact

Impact Statement

A considerable number of patients had a self-report of drug allergy on their medical records, which entails difficulties on their clinical management, and contributes to increase the cost of their treatment.

Introduction

Adverse drug reactions (ADRs) are unintended and potentially harmful drug events that occur at doses frequently used in clinical practice (1). Drug hypersensitivity reactions (DHR) are a type of ADR that is presumed to be immune-mediated and causes reproducible signs and/or symptoms (1) that can be life-threatening, may require or prolong hospitalization, and may impose changes in subsequent therapy (2). They account for 20% of ADRs and are reported in approximately 8% of the general population (3).

DHRs can be divided into immediate reactions, usually occurring within 1 to 6 hours after drug administration, and often presenting with urticaria, angioedema, nasal and ocular pruritus, sneezing, bronchospasm, hypoxemia, hypotension, vomiting, abdominal pain; or nonimmediate reactions, which may start several hours or even days after drug administration and usually present with cutaneous symptoms, such as urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis or severe cutaneous adverse reactions (toxic epidermal necrolysis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms) (2, 4).

Diagnosis is based on medical history, clinical manifestations, and *in vivo* or *in vitro tests* (2). However, overdiagnosis of a drug allergy is common, usually self-reported by patients, and/or incorrectly mistaken for other ADRs. This can become an important limitation for treatments, leading to the use of second-line agents that can be less effective, more expensive, and associated with more side effects (1).

This study aims to evaluate and characterize the frequency of drug allergy in hospitalized patients, and its impact on the patient's treatment.

Material and Methods

A retrospective study was conducted in an Internal Medicine ward, at a tertiary referral center in Lisbon, Portugal. All adult patients admitted between January 2018 and December 2020 with a drug allergy report on their records were included.

The variables gender, age, personal history, drug allergy history, current and previous treatments, clinical evolution during hospitalization, and follow-up after discharge were analyzed. Data were collected from electronic records from both medical and nursing staff.

A complete history of past drug allergy events was considered when there was information about the drug administered, the onset of reaction (immediate if the terms "immediate" or "minutes after" were present on the records, or nonimmediate for reactions described as "late", "several hours", or "days"), and the symptoms developed. Anaphylaxis was considered when there was a report of an immediate reaction with at least two systems involved.

A descriptive statistical analysis was conducted on the data collected. Cost analysis of antibiotic treatment was performed by comparing first-line agents that could have been employed versus the alternative treatment and multiplying by the number of days of use. The cost of each antibiotic was deducted from our hospital pharmacy form. This study was conducted following the approval of the Ethics Committee (CES 1052/2021).

Results

Population

Of a total of 3532 admissions over the 3-year period, 3046 patients were screened, and 470 (15.4%) were selected for having a drug allergy record. Most patients were female (n=276, 58.7%) with a median (P25-75) age of 75 (63-83) years.

Drug characterization

The electronic record of drug allergy was registered in 51.7% (n=243) of patients by the medical staff, and in 84.5% (n=397) by the nursing team. History of allergy to antibiotics was present in 56.4% (n=265) of patients, to non-steroidal anti-inflammatory drugs (NSAIDs) in 21.7% (n=102), and to radiocontrast media (RCM) in 7.0% (n=33). Further details of the suspected agents are represented in table I.

The most common drugs involved were penicillins, followed by salicylic acid, and radiocontrast media. In 14.5% (n=68) of patients, there was a drug allergy report regarding more than one drug class. In 17.9% (n=84) of patients, there were reports of administration of the suspected drug within the hospital setting without developing any adverse reaction.

Reaction characterization

The timing of reaction was described in 50.2% (n=236) of the records, with immediate reactions being the most common (n=199, 84.3%). Mucocutaneous manifestations were the most frequently reported (n=201, 85.2%), followed by respiratory symptoms (n=29, 12.3%) (table II). There were 18 reports of anaphylaxis, 4 of them without mucocutaneous involvement.

Implications on clinical practice

Changes in clinical management directly related to the drug allergy history were verified in 14.5% (n=68): 76.5% (n=52) received a second-line treatment agent, with most cases (n=45) related to the use of alternative antibiotics (table III), and 23.5% (n=16) were denied an exam or procedure, mostly due to the need of radiocontrast administration (n=12). Regarding the group in which an alternative antibiotic was used, 28.9% (n=13) had already received the culprit drug in previous hospital admissions and had developed no reaction. The median (P25-75) of days of use was 7 (3-10) days. This change entailed an increase in the cost of treatment of 2.4 times per patient, compared to the treatment with the drug in avoidance (35.96 *vs*. 14.94 euros per patient treated).

The suspected drug was administered in 14.7% (n=69) of patients: 78.3% (n=54) were antibiotics, 10.1% (n=7) NSAIDs, 2.9%(n=2) RCM, 2.9% (n=2) bronchodilators and 5.8% (n=4) other drugs. In this group, a complete record of past events was present in 49.3% (n=34) of these patients, with 29 reporting immediate symptoms, and 5 describing nonimmediate reactions. After administration of the suspected drug, 87.0% (n=60) of the patients had no reaction and 13.0% (n=9) presented a reaction assumed, by the attending physician, as a hypersensitivity reaction, one of which was anaphylaxis. The reactions' description is presented in table IV.

Follow up

After hospital discharge, 1.9% (n=9) of patients were referred to our Allergy and Clinical Immunology department for an allergy study. Of these, six suspicions were excluded after skin and provocation tests, one was assumed to be angioedema secondary to angiotensin-converting enzyme inhibitor, and two missed their appointments.

Discussion

We found that 15.4% of patients had a record of drug allergy, which is higher than the frequency reported in the general population (approximately 8%) (1), and in a previous study conducted in Portugal regarding self-reported drug allergy (7.8%) (5). This overdiagnosis might be explained by the fact that the population studied refers to inpatients, who are probably more exposed to drugs than the general population and, as such, more prone to develop reactions that can be misinterpreted as a DHR. Another factor that might have contributed was that it is based on self-reports and previous records, that may contain errors or incomplete data. DHRs are often over diagnosed, due to the incorrect use of the term "allergy" in the presence of manifestations possibly from other causes, such as viral infections, expected ADRs, and other conditions nonrelated to drug allergy (2).

Our study showed a female predominance (58.7%), as published in the literature (1,3,6).

We found a clear difference between medical and nursing records, with more allergy reports registered by the nursing team (84.5% vs 51.7%). This difference might be explained by some

hypothesis, namely: 1) the hospital admission is performed by nurses, who have the first contact with the patient, and collect a pool of information, such as previous drug allergies; 2) during the hospital stay, medication is administered by nurses, and patients may recall previous reactions to certain drugs and report them at that time; 3) some reactions reported by patients are not compatible with a DHR, which may lead the physician to omit them from their records more easily than the nurse. We found no other studies in the literature that addressed this aspect.

Regarding drug classes, we found that the most implicated group of drugs were antibiotics (8.7%), particularly beta-lactams, and NSAIDs (3.3%), which is very similar to a recent study where 5.8% of patients self-reported allergy to antibiotics, and 1.5% to NSAIDs (7).

In our population, the most frequent drug allergy report was to penicillins, with a frequency of 6.9%. Recent studies report a prevalence of 5 to 16% in hospitalized patients (8). Even though our result is within this range, it may not correspond to the number of patients with true penicillin allergy, since 70% of subjects with a history of allergy to beta-lactams are confirmed not allergic when submitted to proper tests (4).

NSAIDs-hypersensitivity reports were slightly higher when compared with the general population (3.3% vs. 2% respectively) (9), which might be related to the fact that the study was conducted with inpatients.

Regarding RCM hypersensitivity (1.1%), our results are in line with the reported frequencies of DHRs in 0.5 to 3% of patients receiving nonionic RCM (10). The same applies to multiple drug class allergy reports (2.2%), which are within the estimated values currently published (1 to 10% of patients may have DHRs to distinct and non-cross-reactive drugs) (6).

Immediate reactions and mucocutaneous manifestations were the most frequently reported, in accordance with current literature, where mucocutaneous is the most described system to be affected during DHRs (1). We detected that about half of the records contained incomplete data, regarding the time of onset and symptoms developed during the suspected reaction, which may compromise risk assessment. This description is vital to differentiate between immediate reactions, mostly associated with an IgE mechanism, versus nonimmediate reactions, commonly through a T-cell-dependent mechanism (6, 11, 12). The characterization of signs and symptoms developed, as well as the therapeutic approach, also contribute to improve risk assessment. However, healthcare professionals often register incomplete, or incorrect information when recording a drug allergy in electronic medical records, leading to difficulties in the decision to administer or avoid the drug in question (13).

Patients with an antibiotic hypersensitivity history are often treated with second-line antibiotics, associated with higher risks and costs (8,13). We verified that the allergy labels modified the antibiotic prescribing habits, increasing over 2.4-fold the expected cost of treatment (35.96 *vs*. 14.94 euros per patient). Similar studies have also documented this economic burden on healthcare costs: Li et al. reported that the use of second-line antibiotics, in patients with penicillin allergy

labels, was responsible for an increase between 1.82 to 2.58 times the expected cost of treatment (14). Picard et al. demonstrated an increase of 74% in the cost of treatment of inpatients where an alternative antibiotic was used, due to a history of penicillin allergy (15). Bermingham et al. also found that, in patients with sepsis, the cost of alternative antibiotics was 2.61 times higher, when a label of penicillin allergy was present (16). These data demonstrate the importance of developing delabeling strategies, since they will allow patients to receive first-line treatments and help to reduce healthcare expenses.

More than one-third of our patients, labeled with RCM allergy, were denied an exam requiring RCM administration. On the other hand, of the two patients who were submitted to exams with RCM regardless of their label, one reacted and the other did not. Neither had a description of the RCM administered. Hypersensitivity reactions to RCM are a considerable challenge in clinical practice: the exact name of the agent used is often unknown, and the description of the adverse reaction usually lacks detail. This leads to difficulties in the correct risk assessment and generates uncertainty, resulting in the avoidance of certain procedures (10,17).

Drug provocation test is the gold standard for drug allergy diagnosis (2). The demonstration of tolerance, after the suspected event, is enough to remove the allergy label (18). We verified that 17.9% of patients with current allergy labels had already received and tolerated the drug in question in the hospital setting, allowing the exclusion of the suspected allergy. However, this label was not removed and was still present on their records. This resulted in unnecessary avoidances in 28.9% of the patients, to whom an alternative antibiotic was administered, and might have been prevented if previous records were consulted, or if the label had been removed.

Prompt exclusion of this diagnosis, without a careful and experienced evaluation, may carry danger for the patient, as seen in the one that suffered anaphylaxis after receiving the suspected drug. The other patients, to whom the drug was administered and did not react, may have the allergy label removed so that it does not harm future admissions. This highlights the importance of complete and correct medical records.

Allergy de-labeling, particularly for penicillins, has been demonstrated to be cost-effective versus the use of second-line agents (18,19). To achieve that goal, proper referencing is crucial. However, in our population, it is worth mentioning the very low number of patients referenced for allergy evaluation after hospital discharge (n=9, 1.9%). This poor referencing may have repercussions on future admissions. Some of the reports of suspected allergies can be confirmed, or excluded with appropriate testing, performed by an experienced allergist, either during the hospital stay or after discharge, which would reduce the uncertainty when choosing future therapeutic options for those patients. A better articulation between departments should be encouraged to improve patient management and reduce the healthcare burden of drug allergy labels.

The strength of our study is that it is a descriptive analysis of a large specific population. This might help to provide better estimates of frequency of drug allergy in this group of patients and

contribute to improve their management. It also raises awareness of the negative impact of these labels, and the increase in costs that they represent.

A major limitation of our study is that it depends on self-reports and previous records, which makes us susceptible to errors in the interpretation of episodes, incorrect records, or incomplete data. Another limitation is that it is not a multicentric study, which may not reflect general practices. It would be of interest to conduct similar studies in other centers to compare procedures and adopt better future practices.

Conclusion

A considerable number of patients have a drug allergy label on their electronic medical records. As expected, antibiotics and NSAIDs are the most reported. However, the previous reaction description is missing in about half of them, making a correct risk assessment difficult. This can result in unnecessary avoidances, with increasing complications and healthcare costs, or potentially harmful effects by administration of the suspected drug. A better articulation between departments and proper referencing and diagnosis should be part of the follow-up routine of these patients, contributing to improve both the clinical management and treatment costs in future admissions.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table I Overview of drugs allergies reported on patients' electronic medical records.

Drug	Total (n)	Relative % †	Absolute % ‡
Antibiotics	**265**	**56.4**	**8.7**
Penicillins	209	44.5	6.9
Trimethoprim/sulfamethoxazole	31	6.6	1.0
Quinolones	21	4.5	0.7
Cephalosporins	11	2.3	0.4
Macrolides	10	2.1	0.3
Others	16	3.4	0.5
NSAIDs	**102**	**21.7**	**3.3**
Salicylic acid	37	7.9	1.2
Metamizole	19	4.0	0.6
Ibuprofen	13	2.8	0.4
Diclofenac	10	2.1	0.3
Acetaminophen	9	1.9	0.3
Selective Cyclooxygenase 2 Inhibitor	8	1.7	0.3
Naproxen	5	1.1	0.2
Others	5	1.1	0.2
Radiocontrast media	**33**	**7.0**	**1.1**
Antihypertensive drugs	**23**	**4.9**	**0.7**
Angiotensin converting enzyme inhibitor	11	2.3	0.4
Others	16	3.4	0.5
Antiseptic	**17**	**3.6**	**0.6**
Povidone-iodine	15	3.2	0.5
Others	2	0.4	0.1
Opioids	**16**	**3.4**	**0.5**
Tramadol	16	3.4	0.5
Xanthine-oxidase inhibitors	**10**	**2.1**	**0.3**
Allopurinol	10	2.1	0.3
Others	**84**	**17.9**	**2.8**

Some patients had a record of allergy to more than one drug in the same class.

† Relative frequency in the 470 patients with a drug allergy label.

‡ Absolute frequency in the 3046 patients admitted to the internal medicine ward during this time-period.

Table II Characterization of manifestations according to time of onset.

n = 236	Immediate n (%)	Nonimmediate n (%)
Mucocutaneous	152 (64.4)	35 (14.8)
Respiratory	15 (6.4)	-
Cardiovascular	6 (2.5)	-
Gastrointestinal	8 (3.4)	2 (0.8)
Anaphylaxis	18 (7.6)	-
Total	**199 (84.3)**	**37 (15.7)**

Table III Antibiotics avoided and respective alternative.

Avoided	Alternative used	Total (n)
Penicillins	Cephalosporins	19
Penicillins	Quinolone	9
Penicillins	Piperacillin/tazobactam	5
Penicillins	Carbapenem	3
Penicillins	Lincosamide	3
Penicillins	Macrolide	2
Cephalosporins	Piperacillin/tazobactam	1
Cephalosporins	Carbapenem	1
Trimethoprim/ sulfamethoxazole	Naphthoquinone	1
Glycopeptide	Oxazolidinone	1
Total		**45**

Table IV Reactions' description after re-administration of suspected drugs and comparison with previous event.

Reported culprit drug	Previous reaction	Symptoms	Drug administered	Current reaction	Symptoms
Penicillins	Immediate	Mucocutaneous Respiratory	**Amoxicillin**	Immediate	Cardiovascular Respiratory
Penicillins	Immediate	Mucocutaneous	**Amoxicillin**	Immediate	Mucocutaneous
Penicillins	No Record	No Record	**Piperacillin/ tazobactam**	Nonimmediate	Mucocutaneous
Cephalosporins	Nonimmediate	Mucocutaneous	**Ceftazidime**	Nonimmediate	Mucocutaneous
Trimethoprim/ sulfamethoxazole	Nonimmediate	Mucocutaneous	**Trimethoprim/ sulfamethoxazole**	Nonimmediate	Mucocutaneous
Acetaminophen	Immediate	Mucocutaneous	**Acetaminophen**	Immediate	Mucocutaneous
Ibuprofen	Immediate	Mucocutaneous	**Naproxen**	Nonimmediate	Mucocutaneous
RCM	Immediate	Mucocutaneous	**RCM**	Immediate	Mucocutaneous
Ipratropium bromide	Immediate	Mucocutaneous	**Ipratropium bromide**	Immediate	Mucocutaneous

RCM: Radiocontrast media