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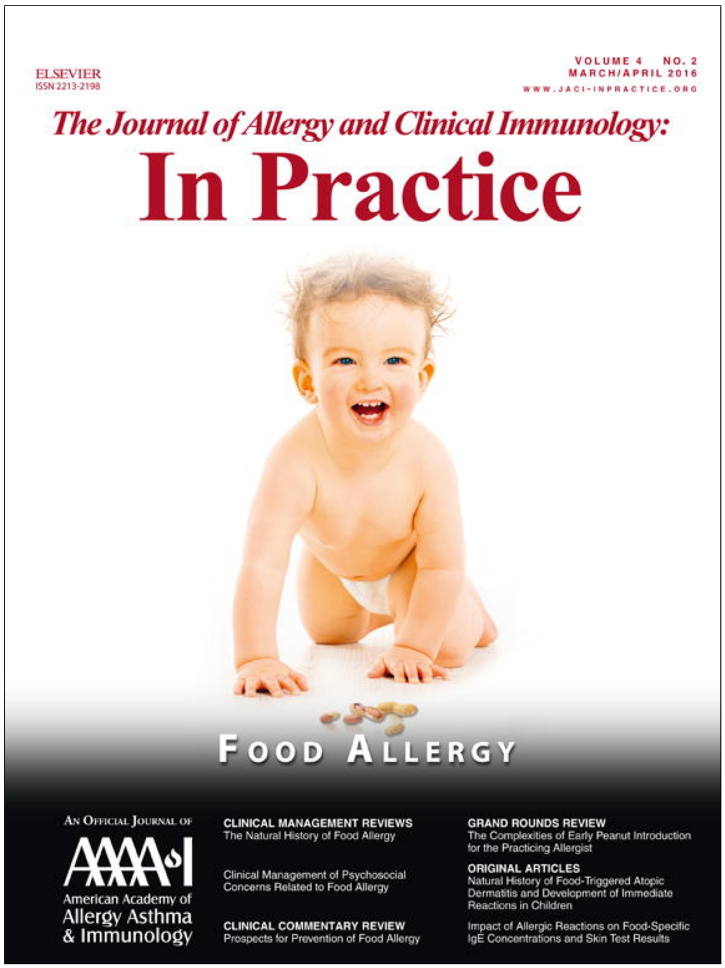

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Original Article

A Predictive Model for the Diagnosis of Allergic Drug Reactions According to the Medical History

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What is already known about this topic? The clinical history is essential when deciding whether to submit patients to controlled drug exposures. Such testing is necessary to rule out sensitization but can be costly and has some risks.

What does this article add to our knowledge? A simple, easy-to-use mathematical model is useful in evaluating potential drug reactions using only the medical history.

How does this study impact current management guidelines? It adds a diagnostic method that estimates the probability of an adverse drug reaction in numerical terms. This may reduce uncertainty about the use of drugs such as penicillin or nonsteroidal anti-inflammatory drugs.

BACKGROUND: Quantification of the risk of an allergic drug reaction through the medical history is essential in clinical decision making. However, in normal clinical practice, this evaluation is generally entirely subjective.
OBJECTIVE: The objective of this study was to construct a mathematical model to predict the risk of allergic drug reactions using the data collected in the medical history.
METHODS: A total of 696 active principles, corresponding to 466 patients aged more than 14 years attending the Allergy Service of the University Hospital of Salamanca, were included. Simple binary logistic regression was used to determine associations between variables from the medical history and the final diagnosis, to construct a predictive model.
RESULTS: Variables useful in predicting a final diagnosis of allergic drug reaction were age, sex, drug class, number of active principles, time to the reaction, number of doses, clinical presentation suggestive of allergic disease, and time to medical consultation. True adverse drug reactions were estimated to occur in 20% of active principles. However, possible allergic reactions could only be ruled out in 52.2%.
CONCLUSIONS: The use of mathematical models could greatly improve the discriminatory capacity of the medical history. Both the overdiagnosis and underdiagnosis of allergic drug reactions should be considered a public health problem. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:292-300)

Key words: *Allergic drug reaction; Drug hypersensitivity; Diagnosis; Predictive model; Penicillin; Analgesics; Medical history*

INTRODUCTION

Allergic drug reactions (ADR) are the third most common reason for consultation in allergy services.[1] Epidemiological data are imprecise. Globally, ADR affect 10%-20% of hospitalized patients and up to 7% of outpatients.[2] However, this might be an underestimate due to underreporting, or an overestimate due to unexplained reactions often being classified as "allergic."[3] This carries risks for the patient. On the one hand, the possibility of anaphylactic shock: 13% of cases are due to drug allergies.[4] On the other hand, the use of therapies that are not first choice treatments and are usually more expensive[5] have more side effects and an increased risk of treatment failure.[6-10] ADR also increase the costs of medical care because of the increased use of emergency services, hospitalizations[10] suspension of tests,[6,7] and extended hospital stays.[8,10]

Assessment by an allergy specialist is crucial because it allows a diagnosis to be reached in some cases and allergies to be ruled out in most patients. Complementary tests include skin tests and laboratory analysis. However, the sensitivity of these diagnostic methods is not optimal, and, in any case, the definitive test to establish or exclude the diagnosis is a controlled exposure test.[11] This may be expensive, time consuming, and potentially dangerous, but is usually necessary, as no sensitization to the drug involved is found in two-thirds of patients with suspected ADR.[11]

Quantification of the risk of ADR by the medical history is vital to decision making by the allergy consultant, and to provide

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Abbreviations used
ADR- Allergic drug reactions
NSAID- nonsteroidal anti-inflammatory drug
SD- Standard deviation

criteria for other physicians to refer the case to a specialist. It may also allow an estimate of the accuracy of suspected diagnoses.

The main objective of this study was to develop a predictive model for the diagnosis of ADR by analysis of all variables routinely collected by the medical history.

METHODS

A retrospective cohort study was performed by the review of the medical history. All patients aged more than 14 years studied for suspected ADR between January 1 and December 31, 2010, at the University Hospital of Salamanca, which provides care to approximately 353,000 persons, were included. Written informed consent was obtained from all patients. Data were entered into a Microsoft Excel database and dissociated to ensure that no patient could be identified.

Two authors assessed and consensually agreed all variables in the medical history that may be useful for the diagnosis of ADR according to previous studies, protocols, and recommendations.[12] The variables finally included were sex, age at the time of reaction, relatives with allergic diseases, personal history of allergic disease, personal history of drug allergy, chronic disease, chronic treatment, skin tests to aeroallergens (pollen, mites, dander, mold), skin test to food allergens (flour, egg, milk, fish, fruit, nuts, legumes), IgE total value higher or lower than the IgE median of 60 found in our sample (IgE60), number of drugs assessed, time to assessment, referring service, emergency department visits, hospitalization, specific drug to be assessed, route of administration, number of doses, clinical manifestations, duration of episode, latency period between exposure and reaction, number of episodes, and previous tolerance (Table I). Candidate variables for inclusion in the multivariate regression model were sex and age, which are routinely included,[13] and variables in Table I with a value of $P < .25$ in the univariate analysis.[13]

Various categories may be established.[1] *Confirmed diagnosis:* when skin tests, specific IgE test, or controlled exposure to the drug are positive. *Diagnosis ruled out:* when the controlled exposure test is negative. *Suspected diagnosis:* suspected according to the medical history but no controlled exposure test is performed. An alternative drug is usually tested. Nonsteroidal anti-inflammatory drugs (NSAIDs) often result in idiosyncratic reactions that are clinically very similar to allergic reactions.[14] Therefore, 2 further categories can be established. *Confirmed diagnosis of idiosyncratic reaction:* when there is a positive oral controlled exposure test to aspirin. *Suspected diagnosis of idiosyncratic reaction:* suspected according to the medical history, but no controlled challenge test is performed.[11]

Statistical analysis

Descriptive variables were analyzed using means and percentages to determine the characteristics of the sample. Binary logistic regression was used to establish possible relationships between the variables contained in the medical history and the final diagnosis to construct a predictive model.[15] The dependent variable was diagnosis confirmed and/or ruled out. Suspected diagnoses and idiosyncratic reactions to NSAIDs were eliminated from the analysis. The statistical study was performed using the SPSS version 21 statistical package. Recommendations on data analysis were followed.[13,15]

RESULTS

Between January 1 and December 31, 2010, 466 patients were tested for ADR. More than 1 suspected active principle was studied in 57.7% of patients. Therefore, 696 active principles were initially studied. A total of 50 patients, representing 70 active principles (10%), abandoned testing because of the large number of medical visits required (mean of 4 visits, with 84% of patients requiring 3 or more visits). Therefore, 626 active principles, representing 416 patients, were finally included in the analysis. The maximum number of active principles studied in 1 patient was 5. A total of 70.7% of the active principles involved were in female patients and 29.3% in males. The mean number of drugs did not differ significantly according to sex ($P = .15$, *t*-test for means).

The mean age at consultation was 48 years, and standard deviation (SD) 17.7. The distribution was normal (Kolmogorov-Smirnov test, $P = .37$). The mean age at presentation of the reaction was 42 years (SD, 18.11), with a normal distribution (Kolmogorov-Smirnov test, $P = 0.44$). The age range was less than 12 months to 89 years. A total of 68.8% of patients were referred from primary health care.

Of the 626 active principles finally evaluated, ADR was ruled out in 58.1% and confirmed in 13.4%, whereas 26.4% remained as suspected. In the remaining 2.1% of cases, a diagnosis of idiosyncratic reactions to NSAIDs was made and confirmed by a controlled exposure test.

With respect to the type of drug, 244 (39%) were NSAIDs, 172 (27.5%) β-lactam antibiotics, and 210 (33.5%) other drug classes (other antibiotics 11.4%, anesthetics 3.5%, corticosteroids 2.9%, opiates 2%, proton pump inhibitors 1.6%, radiocontrast agents 0.4%, and other drug classes 11.8%).

Table II shows the diagnoses assigned according to pharmacological class. In the case of NSAIDs, of the 114 suspected cases, 50 corresponded to ADR and 64 to idiosyncrasies. β-Lactams were the drug class with the most confirmed ADR, and NSAIDs the drug class with the highest sum of confirmed and suspected diagnoses and, therefore, the class with the highest rate of contraindications to their use.

Table III shows the classification of the final diagnosis of the clinical presentations.

To establish associations between the variables included in the medical history and the final diagnosis, simple logistic regression (a single independent variable) was applied to each variable.[13] Candidate variables identified in the first step were IgE median60, number of drugs, time before medical consultation, emergency department visits, drug group, clinical presentation suggestive of allergy, duration of the episode, latency period, and number of doses. Variables not associated with the final diagnosis in the first step were personal or family histories, chronic disease, the number of active treatments, the results of skin tests for aeroallergens and food allergens, the referring medical service, the route of administration, previous tolerance, or the number of episodes.

Of the multivariable models tested, that shown in Table IV was considered the simplest and most useful. After adjustment, IgEmedian60, emergency department visits, and duration of the episode were not considered significant with respect to the final

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TABLE I. Variables used in the medical history of an ADR

Variable	Definition	Final recoding
Demographic		
1. Sex	Sex of patient	Male = 0, female = 1
2. Age at the time of reaction	Patient age when the reactions took place	Years
History		
3. Relatives with allergic diseases	Any reported allergic disease in parents, brothers, or children	Yes/no
4. Personal history of allergic disease	Any reported allergic diseases in patient	Yes/no
5. Personal history of drug allergy	Other reported putative drug allergies in patient, confirmed or not	Yes/no
6. Chronic disease	Description of any pathology lasting ≥ 6 mo coded in ICD-10.	Yes/no
7. Chronic treatment	Number of chronic pharmacological treatments taken daily by patient	Numeric
Skin tests		
8. Aeroallergens	Results of skin test for pollen, mites, dander, and mold	Positive, negative, or unknown/not done
9. Food allergens	Results of skin tests for flour, egg, milk, fish, fruit, nuts, legumes	Positive, negative or unknown/not done
IgE		
10. Total	Analytical value of IgE	Analytical value IgE
11. IgE median 60	Categorized according to median IgE level of this sample (=60 IU)	IgE > 60, <60 or unknown
Attendant circumstances		
12. Quantity of drugs assessed	Total number of active principles studied as suspicious in current consultation	Numeric
13. Elapsed time to assessment	Difference between time of reaction and date of assessment (in allergy clinic)	Consultation before 12 mo = 0/after 12 mo = 1
14. Referring service	Service to which patient is referred	Primary/specialist/unknown
15. Emergency department visits	Number of emergency department visits due to suspected ADR	Numeric
16. Hospitalization	Patient hospitalized or not at time of allergy consultation	Yes/no
Drug		
17. Pharmacological group	Pharmacological group to which active principal studied belongs	NSAIDs/β-lactams/other
18. Route of administration	Way in which the active principle was administered	Parenteral, nonparenteral, unknown
19. Number of doses	Number of doses required to trigger the suspected ADR, counted from the first dose of the last treatment carried out with the active principle	First dose, multiple doses, unknown
Clinical variables		
20. Clinical manifestations compatible with allergic disease	Description of symptoms motivating consultation. If symptoms are compatible with anaphylaxis, angioedema, urticaria, urticaria-angioedema, asthma (chronic or exacerbation), DRESS syndrome, rash (fixed, scaly, maculopapular), or rhinoconjunctivitis, they are considered allergic manifestations. If not, they are considered nonallergic manifestations*	Yes = 0, no =1
21. Duration of episode	Time until the end of the supposed reaction	>24 h/<24 h/unknown
22. Latency period	Time from exposure to the drug to the triggering of the supposed ADR	Immediate, late, unknown
23. Number of episodes	Number of episodes experienced by the patient supposedly due to exposure to the drug	Numeric
24. Previous tolerance	Patient tolerated at least one dose of the active principle in previous treatments with no reaction	Yes/no/unknown

ADR, Allergic drug reactions, *DRESS*, drug reaction with eosinophilia and systemic symptoms; *IU*, international units (for IgE values); *NSAIDs*, nonsteroidal anti-inflammatory drugs.

Classification of manifestations not described in this table as allergic or nonallergic should be made by clinical judgment.

*In this sample, the manifestations considered nonallergic by the allergy clinic were oral thrush, asthenia, pain, eczema, fever with known focus, dizziness, paresthesia of tongue, vagal symptoms, vaginal pruritus, and vomiting.

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TABLE II. Pharmacological classes and final diagnosis

	Final diagnosis								
	Confirmed		Suspect		Ruled out		Idiosyncratic		Total
	N	Percent	N	Percent	N	Percent	N	Percent	N
NSAIDs*	18	7.4	114	46.7	99	40.6	13	5.3	244
β-Lactams†	46	26.7	13	7.6	113	65.7	0	0.0	172
Other drugs‡	20	9.5	38	18.1	152	72.4	0	0.0	210
	84	13.4	165	26.4	364	58.1	13	2.1	626

NSAID, Nonsteroidal anti-inflammatory drug.
*For NSAIDs: The diagnosis was confirmed by skin prick tests with metamizol (11 drugs) and by oral provocation tests in 7 drugs. The diagnosis was ruled out by oral controlled exposure in 99 patients. Intolerance was confirmed by controlled exposure in 13 drugs (12 oral and 1 by inhalation).
†For β-lactams: The diagnosis was confirmed by skin tests in 31 drugs and by controlled exposure tests in 15 drugs (14 oral and 1 by parenteral route). The diagnosis was ruled out in 100 patients by oral controlled exposure tests and in 13 patients by parenteral tests.
‡For other drugs: The diagnosis was confirmed by skin tests in 10 drugs and by oral controlled exposure in 10 patients. The diagnosis was ruled out in 131 reactions by oral exposure tests and in 21 by parenteral exposure.

TABLE III. Clinical presentation and final diagnosis

	Confirmed		Suspect		Ruled out		Confirmed idiosyncratic		Total	
Clinical suspicion	N	Percent*	N	Percent*	N	Percent*	N	Percent*	N	Percent†
Anaphylaxis	1	18.0	25	41.0	23	37.7	2	3.3	61	9.7
Angioedema	9	9.8	34	37.0	43	46.7	6	6.5	92	14.7
Asthma	1	4.3	14	60.9	6	26.1	2	8.7	23	3.7
DRESS syndrome‡	1	9.1	6	54.5	4	36.4	0	0.0	11	1.8
Eczema	2	28.6	0	0.0	5	71.4	0	0.0	7	1.1
FDE§	2	50.0	1	25.0	1	25.0	0	0.0	4	0.6
Rash	17	16.3	1	11.5	75	72.1	0	0.0	104	16.6
Rhinoconjunctivitis	0	0.0	1	50.0	1	50.0	0	0.0	2	0.3
Vagal symptoms	1	3.0	10	30.3	22	66.7	0	0.0	33	5.3
UA‖	9	17.6	15	29.4	26	51.0	1	2.0	51	8.1
Urticaria	30	15.3	42	21.4	122	62.2	2	1.0	196	31.3
Other	1	2.4	5	12.2	36	85.4	0	0.0	41	6.7
Total diagnoses	84	13.4	165	26.4	364	58.1	13	2.1	626	100.0

*Percentage of each clinical suspicion with final diagnosis confirmed, ruled out or suspected.
†Percentage of each clinical suspicion within the total of clinical suspicions.
‡Drug reaction with eosinophilia and systemic symptoms.
§Fixed drug eruption.
‖Urticaria-angioedema.

diagnosis in the second step. The number of drugs involved was not significant but was included in the model because it is a necessary corrective factor of the cluster effect implied by 1 patient having various active principles.

This model found convergence in the fifth iteration, with a global significance of 0.87 in the Hosmer and Lemeshow test. In addition, the model used was validated by evaluating whether the model calculated using a random part (90%) of the sample accurately predicted the remaining 10%. For a cutoff point of 0.5, the model calculated using 90% of the sample correctly classified 81.8% of the active principles. When applied to the remaining 10% of the sample, the model correctly classified 77.5%. The final model shown here was constructed using the global data.

The *a priori* probability of a patient having an ADR or not according to the data from the medical history can be calculated using the following formula (Table IV):

Ln(odds confirmed diagnosis) = −2.533 + sex (female, male) + 0.024 × age − 0.145 × number drugs involved + latency period (immediate, late, do not remember) + No. of initiating doses (first, various, do not remember) + Allergic symptoms (suggestive, not suggestive) + drug class (NSAIDs, β-lactam antibiotics, others) + delay in consultation (first 12 months, later).

For example, a case with a high probability of being confirmed as an ADR in the consultation would be an elderly man (eg, 80 years) who reports a reaction involving only 1 active ingredient and which occurred within the first hour after exposure, with the consultation being made within the first year after the reaction, and with the initial dose of treatment being clearly suggestive of ADR, and the active principle being a β-lactam. The odds ratio would be 6.36, and the probability, expressed as between 0 and 1, would be .864.

To avoid the time needed to perform the calculations for each suspect drug, a Microsoft Excel macro application was developed (in Spanish and English) (see Figure 1), which is also available as a paper questionnaire in Spanish and English. The application is freely available for public bodies and nonprofit bodies (available on request from the Author for Correspondence). This model may be used as a test to establish the hypothetical discriminative capacity

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TABLE IV. Predictive model for a confirmed diagnosis of hypersensitivity

	β*	*P*†	OR‡	95% CI§ Lower	95% CI§ Upper
Sex					
Female = 1, male = 0	−0.226	.490	0.798	0.420	1.515
Age at time of reaction					
Years	0.024	.003	1.025	1.008	1.041
No. of drugs involved					
No. of drugs involved	−0.145	.385	0.865	0.624	1.199
Latency period					
Unknown		.034			
Late	0.758	.049	2.134	1.003	4.539
Immediate	1.116	.011	3.054	1.297	7.193
No. of doses					
Unknown		.034			
First dose	−0.062	.919	0.940	0.286	3.085
Various doses	−0.972	.103	0.378	0.118	1.218
Symptoms suggestive of allergic disease					
Nonallergic symptoms = 1 Allergic symptoms = 0	−1.213	.034	0.297	0.097	0.914
Pharmacological class					
Other drugs		.000			
NSAIDs	0.097	.807	1.102	0.505	2.402
β-Lactams	1.492	.000	4.448	2.205	8.971
Delay in medical consultation					
Consultation < 12 mo = 0 Consultation > 12 mo =1	−0.732	.038	0.481	0.241	0.959
Constant	−2.533	.003	0.079		

NSAIDs, Nonsteroidal anti-inflammatory drug.
*β coefficient.
†Statistical significance.
‡Odds ratio for e^{β}.
§95% confidence intervals.

of the medical history in making a diagnosis. The receiver operating characteristic area of the model calculated for this data set was 0.7685. Time should be taken to test and train for the model in different health care settings before it is used for decision making. As an example, 11 clinical cases reflecting the use of the application have been placed in this article's Online Repository at www.jaci-inpractice.org.

Figure 2 shows that the model classifies all drugs in the sample according to their calculated probability between 0 and 1 (from left to right, from least likely to most likely) and frequency (the higher the height of the column, the greater the number of drugs for this range of probability). Each letter symbolizes 2 drugs. The letter *c* represents confirmed final diagnoses, and the letter *d* diagnoses ruled out. Thus, for example, for a theoretical value of 0.25, in practice 12 active principles in which sensitization was ruled out, and 2 in which it was confirmed, were found. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each cutoff point are shown in Table V. For example, values ≤ 0.5 are considered not ADR, and values > 0.5 as ADR. In this case, the sensitivity of this cutoff is 0.26, the specificity 0.987, the PPV 0.714, and the NPV 0.84.

The model can also be used to estimate the accuracy of suspected diagnoses. Table VI groups active principles according to the final diagnosis. For each active principle, the probability of the risk, and the minimum value, maximum value, mean, and SD according to diagnostic groups are calculated. Thus, although the final diagnosis is known, the previous probability assigned by the model is shown. The results show that the mean value of risk in patients with a suspected diagnosis is equal to that of the total population before complementary testing (0.198).

DISCUSSION, LIMITATIONS, AND CONCLUSIONS

Estimating the risk of disease using mathematical models has limitations, both methodological and of data quality, that make it difficult to estimate individual risk. There may also be differences between populations that affect the calculations. However, accuracy is greater and more scientific when evaluation is systematic and verifiable, and is very successful in predictions concerning populations.[13] However, the use of models alone will never be sufficient as many other factors would need to be in place (patient and clinician education, appropriate time and infrastructure, evidence base for controlled challenges of lower risk patients, etc.). To construct a model that could successfully predict ADR in a larger population, such as Europe, multicenter studies with larger numbers of patients, further investigation of useful variables, and more accurate definition and standardization of the variables included here would be necessary. The results of this study, and empirical use in our allergy clinic, suggest that the model presented here, although requiring external validation, permits quantification of the risk of an allergic reaction with a known margin of error, which is not possible using subjective impressions, and may represent a step on the way to defining a universal test whose diagnostic power could be compared with skin tests or controlled exposure. However, the successful use of mathematical models in clinical practice must take into account other factors such as the education and training of physicians and patients, and adequate means to ensure implementation. For example, type A reactions, which account for around 80% of ADR, are normally predictable, dose dependent, and related to the pharmacological actions of drugs,[16] whereas type B reactions, which account for around 15% of ADR, are normally unpredictable, and not dose dependent and involve hypersensitivity due to nonspecific mechanisms or specific immune reactions.[17] However, type A reactions may have a genetic component, whereas type B reactions may be T cell mediated and dose dependent. These complexities are, currently, often poorly covered in medical education. The most reliable place to apply this tool for many reactions might be prospectively when seeing a patient with an ADR and before a label gets into the medical record. Therefore, external validation of this model in other settings, both geographical and medical (primary care, allergy clinics, and nonallergy specialists) will provide essential new information. Currently, the results of the study are only applicable to the Allergy Clinic of Salamanca.

This study used data from usual clinical practice and found a rate of suspected diagnoses of 26.7%. In the analysis, these diagnoses were, in fact, lost data (after testing they should be either confirmed or ruled out) and represent a selection bias. However, the calculations suggest that, as there were not many differences with the global sample, the proportion of expected confirmed cases in the general population and the population with a suspected diagnosis is the same, meaning that the clinical characteristics of the 2 populations, after determination and

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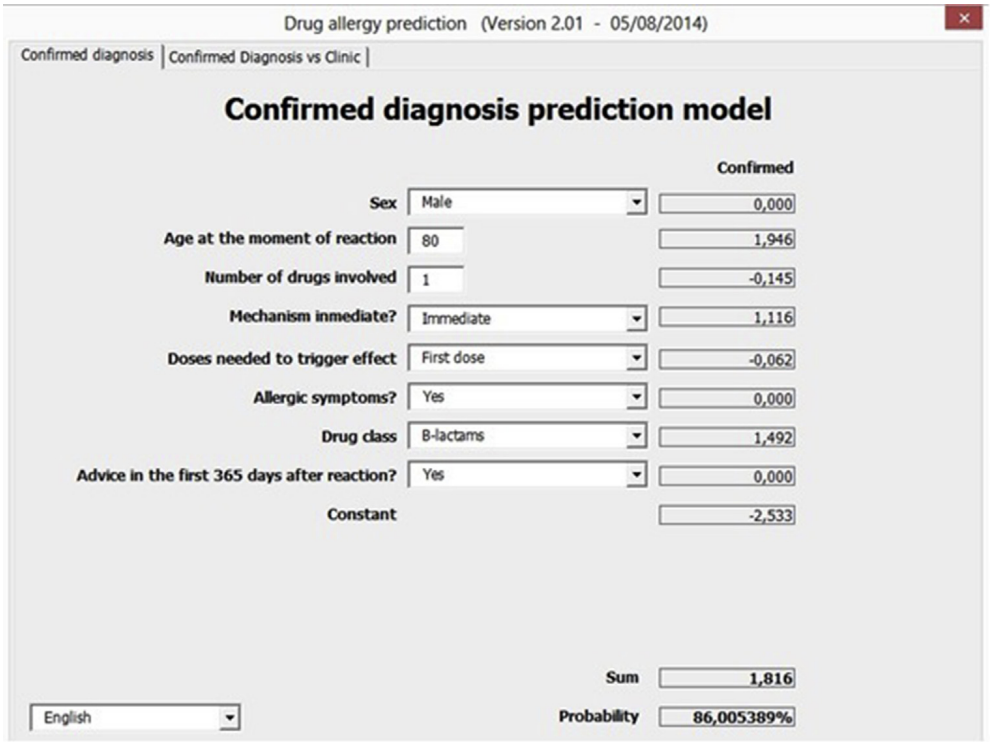

FIGURE 1. Software for calculation of probabilities of confirmed diagnosis.

quantification of the variables associated with the diagnosis, did not differ substantially (Table VI), and the bias was not sufficiently large enough to invalidate the model. In any case, this could only be corrected for by reaching a final diagnosis in the whole study population, which would be difficult in large cohorts.

In the model constructed, what should be the cutoff point for considering or ruling out an ADR? In our sample, there was no case in which an ADR had been ruled out when the calculated probability was $\geq$.75. In these cases, it would be reasonable to assign a diagnosis of suspicion. In contrast, an NPV = 1 was not obtained until the calculated probability was .04. We suggest that if the initial clinical presentation is not severe, and has a low probability in the model ($\leq$.1), and the patient is clinically stable, a controlled exposure test may be made directly. This could significantly shorten the diagnostic process in up to 40% of active principles that are not ADRs and take adequate precautionary measures in 92% of those that are ADRs, as this cutoff point has values of specificity (the percentage of healthy people who are correctly identified as not having the condition) and sensitivity (the percentage of sick people who are correctly identified as having the condition) of 0.405 and 0.922, respectively (see Table V). However, these are only general suggestions for our setting and for ruling out allergic reactions. In the end, the cutoff point should be determined by the risks that physicians and patients can and must assume.

Cases in which the calculated probability is >.1 should generally be treated by a specialist. In cases with a calculated probability <.75, allergy consultants should recognize the risk and should, at least, carry out skin tests. However if, as frequently occurs, no protocol for controlled exposure testing is available, the patient is not willing to do it or the means are not available, we recommend that time and money should not be wasted on further tests and probability models should be applied. The patient should be informed that the reaction may not be due to an ADR, the diagnostic process has not concluded, and an alternative therapeutic option might be offered.

The mean pretest probability of the cases diagnosed as suspected in our series is exactly the same as the mean for the total population (.198) (Table VI). This would indicate that a suspected diagnosis made by an allergy specialist is not more accurate than that made by the referring physician: the expected proportion of real cases of allergy in the initial population and those labeled as suspicious at the end of the study is the same. Likewise, the mean pretest probability of the cases diagnosed as confirmed was only .34. This value suggests that it is very difficult to rule out a diagnosis of ADR using the medical history, even when clinical manifestations are not suggestive of an ADR. Complementary tests will be necessary in most cases to provide a sufficient level of evidence.

In the Spanish *Alergológica 2005* epidemiological study of ADR,[1] the diagnosis was confirmed in 26.6% of reactions, ruled out in 37.2%, and remained as suspected in 36.2%. Thus, suspected diagnoses were more common than confirmed diagnoses. This, together with the supposed prevalence of ADR, suggests that overdiagnosis is a public health problem in Spain. In our series, more diagnoses than the national mean were ruled out. This is probably due to classification bias among professional observers, that is, clinical variability due to differences in the medical history, the observation of patients, and their diagnostic and/or therapeutic classification. In the *Alergológica 2005* study, the diagnosis was ruled out in 20% of the reactions,

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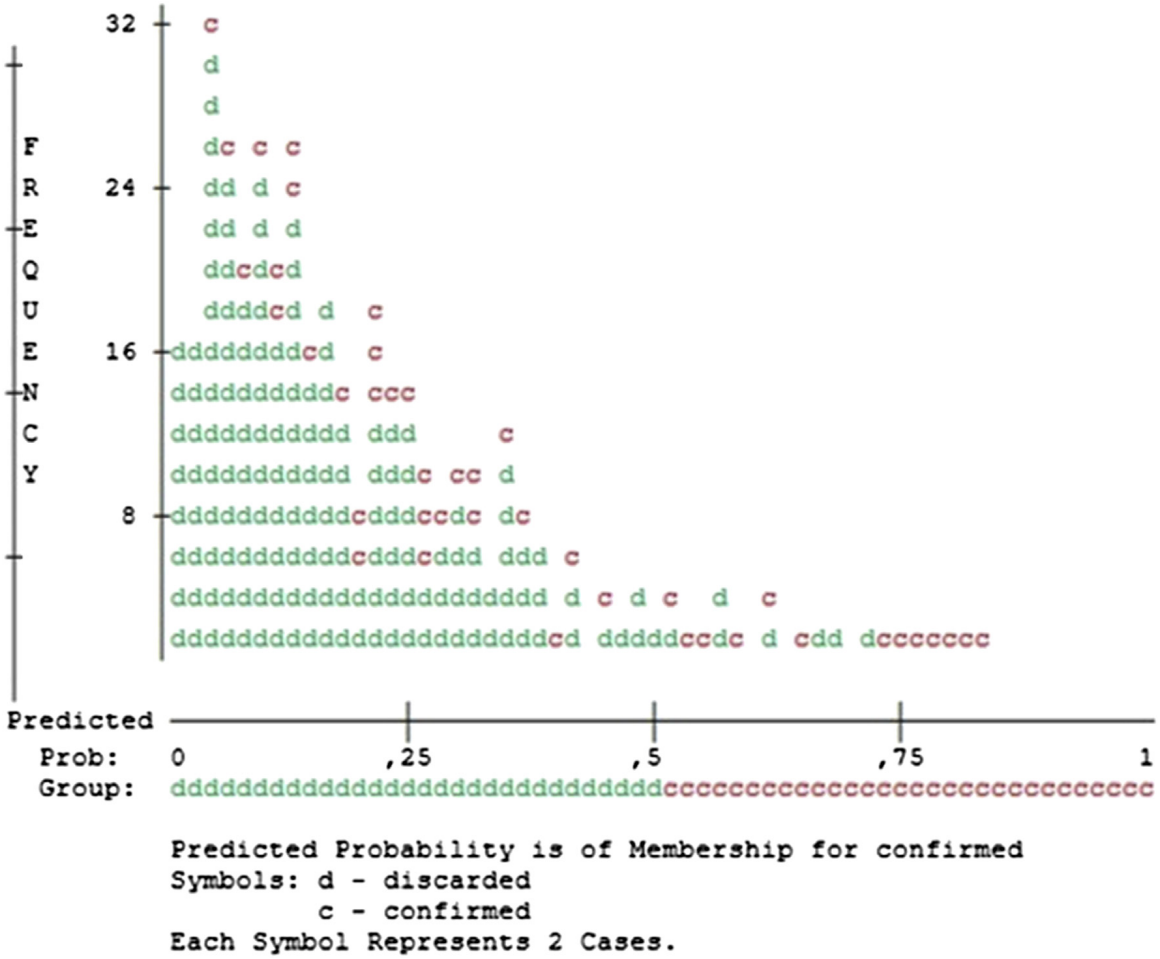

FIGURE 2. Classification of active ingredients according to the probabilities of the model.

TABLE V. Sensitivity, specificity, positive predictive value, and negative predictive value for different cutoffs*

	0.04	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5	0.6	0.7	0.75
Sensitivity	1	0.974	0.922	0.779	0.701	0.584	0.481	0.351	0.26	0.156	0.104	0.065
Specificity	0.139	0.194	0.405	0.57	0.676	0.786	0.845	0.942	0.974	0.987	0.997	1
PPV	0.224	0.231	0.278	0.31	0.35	0.405	0.435	0.6	0.714	0.75	0.889	1
NPV	1	0.968	0.954	0.912	0.9	0.883	0.867	0.853	0.84	0.824	0.817	0.81

NPV, Negative predictive value; *PPV*, positive predictive value.
*Negative: equal to or less than these values (test predicts no allergic drug reactions [ADR]); positive: higher than these values (presence of ADR).

TABLE VI. Pretest probability of each diagnostic group between 0 and 1 based on the model

Final diagnosis	N*	Percent†	Minimum probability	Maximum probability	Mean probability	Standard deviation
ADR confirmed	77	14.2	.04	.82	.34	0.21
ADR suspected	145	26.7	.01	.79	.20	0.14
ADR ruled out	309	56.8	.01	.70	.16	0.13
Idiosyncratic	13	2.4	.10	.49	.22	0.10
Total	544	100	.01	.82	.20	0.16

*Total number of active principles for each diagnostic category.
†Percentage of total.

confirmed in 34%, and suspected in 46% with respect to NSAIDs and confirmed in 29% of reactions, ruled out in 42%, and suspected in 29% with respect to β-lactams.

It has been postulated that, unlike other allergic diseases, genetic influences are not so important in the case of ADR and that sensitization is principally due to exposure.[18] Our results show

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that the family history of allergic disease (OR: 1.060, CI: 0.559-2.008), the personal history of allergic disease (OR: 0.992, CI: 0.603-1.634), and the personal history of ADR (OR: 1.347, CI: 0.691-2.624) did not influence confirmed diagnoses, and therefore these variables were not included in the model. However, Roujeau et al[19] found that 25.6% of adolescents whose parents had suffered an allergic reaction to antibiotics also had an allergic reaction to an antibiotic, compared with only 1.7% of adolescents whose parents had not had such a reaction. The differences observed in our results may be explained by both overdiagnosis and underdiagnosis: false-positive suspected diagnoses and undiagnosed cases would weaken the association. Improvements in the description of reactions and care to define exposure and effect could demonstrate the association with the familiar history.

With respect to the rate of underdiagnosis, there were a majority of females in our series. However, the difference between sexes with respect to confirmed diagnoses was not significant after adjusting in the multivariate analysis. This suggests that there may be a considerable number of undiagnosed ADR in the general population, principally in males who have not sought consultation.

The latency period was divided into 3 categories: "immediate" (occurred in the first hour), "late" (occurred later), and "unknown" (the patient did not remember the time elapsed). Overall, this variable was significant ($P = .034$), but the principal difference occurred in the "unknown" group compared with the other 2 groups. The same is true for the variable number of doses ($P = .034$) (Table IV). Patients who are really allergic tend to remember the details of the reaction, including the latency period and number of doses of the last treatment taken before the reaction occurred, more clearly. The "immediate" category had a slight nonsignificant advantage compared with the "late" period, possibly due to greater ease in establishing cause and effect, but not to a greater frequency. Therefore, in reality, the immunologic mechanisms of the categories may overlap considerably in time or may not be clearly differentiated by the medical history.[20]

With respect to the dichotomous variable "clinical manifestations suggestive of hypersensitivity reactions," overall this variable was less strongly associated with confirmed diagnoses than age at the moment of reaction and drug class, even though all confirmed allergic reactions must, by definition, be accompanied by a clinical presentation of hypersensitivity. However, even if it seems clear that there is an allergy, the cause may not be the drug and, conversely, reactions that do not seem to be allergic may eventually be confirmed. Improvements in the medical history and in the exact description of the clinical presentation will be aided by accurate knowledge of the attending circumstances and the differential diagnosis.

NSAIDs are the drugs most commonly implicated in studies on hypersensitivity reactions, followed by β-lactam antibiotics.[21] However, after adjustment for the variable "pharmacological class" β-lactams were the major cause of allergies. The estimated proportion of true allergic reactions was 32% for β-lactams and less than 17.4% for NSAIDs. The model calculates only the probability of selective allergy and is constructed to deliberately eliminate the few confirmed records of idiosyncrasies. This means that an idiosyncratic reaction may count as an allergy, and, therefore, the above totals may correspond, in part, to idiosyncratic reactions, which is why we state "less than 17.4%." This was done to facilitate the work of interconsulting physicians, who would, presumably, withdraw the drug even without knowing the type of reaction, which can be distinguished by the allergy specialist. The study of idiosyncratic reactions to NSAIDs exceeds the scope of this study, but we believe that there is also substantial overdiagnosis when the medical history is used and that more exposure tests should be carried out. Withdrawal of drugs or strict limitations on the dose reduces the therapy available for pain relief considerably. In certain situations, NSAIDs should be considered essential. The correct management of these reactions requires further research.[22] In our study, most diagnoses of idiosyncratic reactions were made exclusively by the medical history. There were 64 cases of withdrawal of therapy after the medical history versus 13 confirmed cases of idiosyncratic reactions.

In conclusion, our results show that it is feasible to construct mathematical models for the predicted risk of ADR using data from the medical history. The use of models would improve the capacity of discrimination and have implications for the quality of care and patient safety. The overdiagnosis of drug allergies should be regarded as a public health problem. Further research is needed to determine how primary care could be more closely involved in ruling out drug hypersensitivity by performing controlled exposure tests for cases of low-risk reactions. Allergy clinics could provide a better assessment of the real risk and thus adjust the number of suspected diagnoses.

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APPENDIX

Individual Clinical Cases and Population Management

Introduction. This appendix presents 11 real clinical cases that have been observed in the last 24 months and their current treatments as examples of how to use a risk prediction scale in daily practice. None of them has been seen in the Allergy Department of Salamanca, suggesting that the scale may be used in other contexts.

The clinical cases show the actual actions taken. The comments refer to how correct risk quantification could have improved treatment, even in the case of GPs, for example, in whom the knowledge of allergic reactions may be limited.

Case reports

Case 1: Seen in primary care. Suspected β-lactam allergy. Salamanca city. A 17-year-old male patient consulted our clinic with symptoms including sore throat, tonsillar hypertrophy, fever, sores in the mouth and penis, and generalized skin rash after taking several doses of amoxicillin. Symptoms appeared more than an hour after administration of the last dose. Amoxicillin was withdrawn. EBV serology was positive.

At 10 months, the patient consulted our clinic and presented with exudative pharyngitis. The patient did not want to take erythromycin (the alternative drug) due to a nonspecified liver problem.

The GP believed that the rash was due to mononucleosis, and that the risk of hypersensitivity was low, and prescribed amoxicillin. The patient agreed and took the first dose at home.

The GP considered that the symptoms were not suggestive of an allergic reaction and that the most likely etiology was EBV. In such a case, the theoretical risk of allergic sensitization is less than 10%. If there were real allergic sensitization, provocation of the rash again in a controlled situation would not be a serious health risk. It is reasonable to perform a controlled exposure test. Our assessment is that it would have been correct to prescribe amoxicillin provided the first dose had been taken in the health center with no signs of illness present.

Case 2: Seen in primary care. Suspected allergy to β-lactam. Salamanca city. A 65-year-old woman attended her health center for another reason. She claimed to be allergic to amoxicillin because, on the one occasion she took it, she felt "very ill" (literal words). She did not remember the exact symptoms, or if they occurred with the first dose or within the first hour. She did remember that she had no respiratory symptoms or skin or mucous membrane manifestations. She did not remember her age when this occurred but believed that she was approximately 43. She had never been studied by an allergy clinic.

The calculation yields a value of 9.03% and the symptoms presented were mild and occurred long ago. Therefore, we consider it reasonable to study the patient in her health center with a controlled exposure test, without referral to an allergy clinic. However, the treating GP did not wish to do so due to lack of time.

Case 3: Seen in hospital ER. Suspected allergy to β-lactam. Salamanca city. A 60-year-old woman attended the hospital emergency department with pain in the renal fossa and fever, and was diagnosed with acute pyelonephritis.

When asked if she was allergic to drugs, she replied that she suffered malaise after taking amoxicillin approximately 15 years ago. She did not remember if it was after the first dose, or how soon the symptoms were triggered. She had no cutaneous symptoms or breathing difficulties and did not consult a doctor about the problem.

The patient was admitted to hospital for, among other things, better adjustment of empirical antibiotic therapy.

This was not the best time to examine the alleged allergy, but having not done so in a baseline situation conditioned treatment and, probably, her hospitalization. Ambulatory control was more difficult as β-lactam antibiotics could not be prescribed. The real risk of allergy was low (9.44%).

Case 4: Reported by a primary care nurse. Suspected allergy to β-lactam. Caceres province. This case was reported by a primary care nurse. Today, the nurse is 55 and the events took place at the age of 25. Thirty years later, the patient still remembers the events clearly. She suffered from acute pharyngitis for which amoxicillin was prescribed. After the first dose of treatment, and within the first hour, the patient presented with diarrhea, malaise, and flushing. She consulted the prescribing physician within 24 hours, but the physician believed that the patient was not allergic because she had taken amoxicillin previously with good tolerance and without the typical side effects. She was not referred to an allergy clinic. Even so, she decided to stop taking the medication. After 4 days with no improvement in the acute pharyngitis, the patient decided to restart amoxicillin, but had the foresight to do it at home surrounded by the family. Urticaria, respiratory distress, and hypotension were triggered almost instantaneously. The patient was taken to the emergency department where anaphylactic shock secondary to amoxicillin was diagnosed. At that time, she was told not to take β-lactams and to take precautions when handling them.

This anaphylaxis could have been avoided with proper risk quantification. Despite not having presented with typical symptoms of allergy, the risk was 27.7%. According to our recommendations, the taking of medications should have been immediately suspended, and the patient referred to specialized care.

In this case, the patient performed their own "controlled exposure test." This attitude is very frequent when the clinical response does not satisfy patients. Anyway, the majority of patients with a remote history of anaphylaxis decades later would tolerate at least 1 drug in the β-lactam class, and this would have been an indication for allergist consultation and detailed intradermal test/skin prick test and oral challenge.

Case 5: Seen by allergy clinic. Suspected allergy—idiosyncratic reaction to NSAIDs. Madrid city. A 27-year-old patient was allergic to grass pollens, with moderate-severe seasonal rhinoconjunctivitis since childhood. He decided to undergo immunotherapy. The specialist prescribed parenteral immunotherapy against grass pollens.

The patient began vaccination in the health center, with increasing weekly doses of intramuscular injections, and reached the maintenance dose without problems.

Intercurrently, the patient was suffering from catarrh and took an anti-influenza preparation (aspirin, phenylephrine, chlorpheniramine) for several days. On the third day, the patient suffered an episode of malaise, numbness, and swelling of the right upper lip, which was triggered torpidly more than an hour after taking the medication. The patient did not consult for this

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episode nor gave it any importance and it resolved spontaneously. Immunotherapy continued with normality.

After a month, the patient suffered catarrh again and took the same influenza preparation again. After 36 hours and 5 doses, the patient suffered a clear episode of angioedema, with significant inflammation of both lips, but without respiratory difficulties.

The patient requested an urgent visit with the GP, who prescribed no medicine or advice, and referred the patient to a specialist with a request to be seen within 7 days.

On the same day, the patient finally attended the emergency department and was administered a dose of intramuscular methylprednisolone.

The allergy clinic specialist did not believe that this was a side effect of the vaccine. The most common cause of spontaneous angioedema is anisakis, and therefore the specialist advised against eating fish and using the influenza preparation. The patient was referred to hospital for study. The immunization schedule was not suspended at any time. The patient attended the reference hospital, missing a morning's work. After an initial history was taken, the patient was told to return 3 more times, that is, implying the loss of 3 further working days, to have tests made and receive the results.

He became tired of the process, threw the box with the immunotherapy into the rubbish bin, and no longer took aspirin.

Eight years later, the patient has not stopped eating fish, has sometimes taken other NSAIDs (ibuprofen) without side effects, and has tried oral immunotherapy prescribed by another allergist.

The seasonal rhinoconjunctivitis has improved, and the patient has not presented with any episodes of angioedema in recent years.

The GP did not know how to treat angioedema, which resulted in an emergency department visit.

In this complex case, the cause of the angioedema will probably never be known, but we can suggest that it is unlikely to have been due to aspirin (calculated probability of 8.1%). The patient himself ruled out an idiosyncratic reaction to NSAIDs by using ibuprofen and to an allergy to anisakis by not removing any type of fish from the diet. The quantification of risk by the history could shorten the diagnostic process. The allergist (or even the GP) could have carried out a controlled exposure to aspirin, avoiding 4 consultations, with all they entailed.

Case 6: Seen in primary care. Drugs other than NSAIDs and β-lactams. Cáceres province. A 55-year-old patient from an ethnic minority was diagnosed with hypertension and type II diabetes mellitus. He had bad glycemic control with metformin monotherapy. The GP decided to add a DPP-4 inhibitor (sitagliptin). The patient returned to the GP complaining of a suffocating sensation after taking the medication, and said he felt allergic to the medication and would not continue taking it.

The medical history is difficult due to the vehemence of the patient, but apparently the same thing occurred when hypertensive medication was introduced. There were no cutaneous manifestations at any time.

The GP added another DPP-4 inhibitor (vildagliptin).

The patient returned to the GP with the containers of medications that, he said, should be given to other patients. The patient was experiencing the same sensations of suffocation and was convinced of an allergy to all DPP-4 inhibitors.

This case shows that a scale may not be applicable in all situations. The elevated psychological component in this patient means the anamnesis cannot be considered valuable.

Case 7: Seen by allergy clinic. Suspected allergy to NSAIDs. Valladolid city. A 50-year-old patient reported a medical visit a month previously after taking 2 tablets of oral metamizol for the treatment of low back pain, with the presentation of palmar pruritus and interdigital inflammation of the forearm, dysphagia, and dyspnea less than 1 hour later. The patient attended the emergency department and was given an injection of methylprednisolone: the symptoms resolved within 48 hours. The patient subsequently tolerated paracetamol.

Personal history: intervention of septum. No history of allergic disease.

Probability of allergy to metamizol according to medical history: 19%.

Investigations: intraepidermal and intradermal tests for metamizol with positive intradermal tests to metamizol.

Clinical judgment: angioedema due to hypersensitivity to metamizol.

Treatment: administration of metamizol and pyrazolone anti-inflammatory drugs ruled out.

Review: not required.

In this patient, the study was completed, the referral was correct, and it was reasonable to continue the study until the end and not assign a suspected diagnosis.

Case 8: Seen by allergy clinic. Suspected allergy to β-lactam. Valladolid city. A 37-year-old patient presented with nausea, vomiting, palmoplantar pruritus, and unconsciousness for a few minutes 2 months previously while receiving a first dose of i.v. amoxicillin-clavulanate for the treatment of acute pyelonephritis.

Probability of amoxicillin allergy according to the medical history: 65.12%: probability of clavulanic allergy: 30%.

Investigations: intraepidermal tests to penicilloyl-polylysine (PPL), minor determinant mixture (MDM), penicillin, amoxicillin, amoxicillin-clavulanate acid, with positive results for MDM 5×5, amoxicillin 5×5, amoxicillin-clavulanate 5×5. Negative for PPL.

Clinical judgment: anaphylactic due to hypersensitivity to amoxicillin.

Treatment: administration of β-lactam antibiotics (penicillin, aminopenicillin, cephalosporins, carbapenems, and monobactams) ruled out at that time.

There was a high probability of a confirmed diagnosis of amoxicillin allergy when the study was completed. Two drugs, amoxicillin and clavulanic acid, were studied.

In further consultations, tolerance to alternative β-lactams should be studied.

Case 9: Seen by allergy clinic. Suspected allergy to β-lactam. Valladolid city. A 62-year-old patient had, 22 years previously, presented with pruritus and micropapular erythematous lesions over all the skin, 3 days after administration of an oral penicillin derivative for the treatment of fever. No angioedema, respiratory difficulties, loss of consciousness, or digestive symptoms were reported. The GP recommended suspending the treatment. The patient attended

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our allergy clinic in 1997 and 2000: positive results for intraepidermal and scarification tests to penicillin were found.

Probability of allergy to amoxicillin according to medical history: 23.9%.

Allergy study: intraepidermal and intradermal skin tests against PPL, MDM, benzypenicillin, amoxicillin, amoxicillin-clavulanate, and cephalosporin were negative.

Oral controlled exposure test with phenoxymethylpenicillin (penilevel): tolerated at therapeutic doses.

Skin tests and rechallenge with phenoxymethylpenicillin (penilevel) at 3 weeks were negative.

Clinical judgment: current penicillin allergy ruled out.

Treatment: not required.

Review: not required.

This patient was suggested to be allergic using a skin scarification technique, which is very sensitive but not very specific, and had undergone a provocation test. Restudy showed that the estimated risk was not excessively high and the diagnosis was worth reconsidering. New investigations were made and allergic sensitization was ruled out.

Case 10: Seen by allergy clinic. Suspected allergy to β-lactam. Valladolid city. A 66-year-old patient reported having had pruritus from the head to the toes, sweating, nausea, and syncope some 15 minutes after administration of the first dose of amoxicillin-clavulanate for the treatment of sinusitis. The patient attended the emergency department and was administered methylprednisolone, which resulted in improvement of the symptoms.

Probability of allergy to amoxicillin allergy: 79.1%, and to clavulanate: 45.95%.

Investigations: intraepidermal tests to PPL, MDM, penicillin, amoxicillin, amoxicillin-clavulanate, and cephalosporin with positive results for amoxicillin 5×5 and amoxicillin-clavulanate 5×5.

Clinical judgment: anaphylaxis due to allergy to amoxicillin-clavulanate.

Treatment: administration of β-lactam antibiotics ruled out at this moment.

The patient eventually proved to be allergic to amoxicillin. The patient was studied until the end, but it would have also been reasonable, given such a high estimated risk, to have assigned a diagnosis of suspicion from the outset and thus have shortened the whole diagnostic process. In subsequent consultations, tolerance of alternative β-lactams should be studied.

Case 11: Seen by allergy clinic. Suspected allergy to NSAIDs. Valladolid city. A 66-year-old patient was administered diclofenac gel for the treatment of tendinitis in the shoulder. After 12 hours, the patient suffered erythema and papular-erythematosus pruritic lesions where the gel was administered and intense bilateral palpebral edema. The patient's GP prescribed antihistamines and topical corticosteroids resulting in improvement in 2-3 days and subsequent flaking. The patient subsequently tolerated ibuprofen and paracetamol.

Probability of allergy to diclofenac: 37.2%.

Investigations: intraepidermal tests against diclofenac were negative. Patch tests with diclofenac, aspirin, indomethacin, and ibuprofen were positive at 46 and 96 hours with diclofenac and were negative for other allergens tested.

Clinical judgment: fixed drug eruption due to allergy to diclofenac.

Treatment: administration of NSAIDs derived from acetic acid ruled out.

In this case, sensitization to diclofenac was confirmed. The estimate of risk was fairly high, even though this was a late reaction to an NSAID.

Management in Specialized Allergy Clinics

In the Hospital Río Hortega de Valladolid, the pressure on care for ADR is a major management challenge. There is a long waiting list and ensuring that referrals from primary care are correct would largely alleviate the problem.

Being able to quantify the risk has allowed us to reduce consultations. In many patients with mild reactions and low risk, a controlled exposure test is performed at the first visit and ruled out.

Risk estimation allows us to group patients with known probabilities. This allows controlled exposure tests to be made in big groups of low-risk patients on the same day. However, this is not advisable in high-risk patients, whose groups should be smaller or even studied individually.

On one occasion, our reagents broke down, leading to false positives. The repetition of positives in low-risk patients allowed this situation to be suspected, checked, and corrected.

If, in spite of everything, a diagnosis of suspicion must be assigned, this should be accompanied by a quantitative estimate that will allow evaluation of posterior situations of risk benefit. Likewise, diagnoses of suspicion will be more frequently assigned to patients with real allergies.

Management in Primary Care

We are currently working on a joint guide for primary care physicians in our region. This will include the written test presented in the article as a guide. We hope to perform a validation study for our region in the future.

Many primary care physicians are reticent to make controlled exposure tests in low-risk patients, or to refer them to allergy clinics. Many patients remain unstudied in one way or another. We have observed in the clinical cases presented above that it is common to test exposure to the suspected drug in the patient's home, with the risks that this entails, or excessive caution without seeking other alternatives. This is a service that a specialist allergy clinic should be able to provide and help to provide to GPs.