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ORIGINAL ARTICLE



A clinical decision-making algorithm for penicillin allergy

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ABSTRACT

Background: About 10% of subjects report suspected penicillin allergy, but 85–90% of these patients are not truly allergic and could safely receive beta-lactam antibiotics

Objective: To design and validate a clinical decision-making algorithm, based on anamnesis (chronology, severity, and duration of the suspected allergic reactions) and reaching a 100% sensitivity and negative predictive value, to assess allergy risk related to a penicillin prescription in general practise.

Study design and methods: All patients were included prospectively and explored based on ENDA/EAACI recommendations. Results of penicillin allergy work-up (gold standard) were compared with results of the algorithm.

Results: Allergological work-up diagnosed penicillin hypersensitivity in 41/259 patients (15.8%) [95% CI: 11.5–20.3]. Three of these patients were diagnosed as having immediate-type hypersensitivity to penicillin, but had been misdiagnosed as low risk patients using the clinical algorithm. Thus, the sensitivity and negative predictive value of the algorithm were 92.7% [95% CI: 80.1–98.5] and 96.3% [95% CI: 89.6–99.2], respectively, and the probability that a patient with true penicillin allergy had been misclassified was 3.7% [95% CI: 0.8–10.4].

Conclusions: Although the risk of misclassification is low, we cannot recommend the use of this algorithm in general practice. However, the algorithm can be useful in emergency situations in hospital settings.

KEY MESSAGES

- True penicillin allergy is considerably lower than alleged penicillin allergy (15.8%; 41 of the 259 patients with suspected penicillin allergy). A clinical algorithm based on the patient's clinical history of the supposed allergic event to penicillin misclassified 3/41 (3.7%) truly allergic patients.

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Clinical decisional algorithm; penicillin allergy; risk of allergy

Introduction

Many patients reporting skin rash (urticaria, exanthema etc.) when treated with beta-lactams, penicillins especially, are automatically considered “allergic to penicillin”, and do not receive further treatments with these antibiotics, even when they are useful or mandatory. The prevalence of allergy to penicillin and beta-lactam antibiotics in the general population is unknown. About 10% of individuals report a suspected allergy to penicillin, but studies based on results of allergological work-ups have shown that 85–90% of these patients are not truly allergic and could safely receive beta-lactams [1]. The estimated penicillin allergy in the general population is about 1 and 2% [2,3].

The additional cost induced by treatments with alternate antibiotics was estimated to be 63 times greater for hospitalized patients who are considered allergic than for non-allergic patients [4–6]. Moreover, treatments with alternate antibiotics may lead to selection of multiresistant microorganisms, to lengthening of treatments with these antibiotics and/or of hospitalizations, and to increase in the number of antibiotic treatments and of hospitalizations.

In this study, we aimed to design and validate a clinical decision-making algorithm for general practitioners who have to treat patients with a suspected penicillin allergy to help them in assessing the allergy risk in the event of a penicillin prescription.

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Patients and methods

Study design

For the validation of a clinical decision-making algorithm for penicillin allergy, physicians classified patients by using the algorithm at the end of the anamnestic consultation and before performing allergy work-up. This classification was not considered as determinant for the subsequent allergy work-up. Penicillin allergy exploration results were used as the gold standard to define a penicillin allergy, as previously reported [7]. Results of penicillin allergy explorations (gold standard) were compared with results of the algorithm, for each patient. The algorithm was validated *a posteriori* and the usual care and allergy explorations were not influenced by the algorithm's classification. This was an observational study and patient informed consent was obtained, in accordance with local ethic committee.

Elaboration of the algorithm

The algorithm was set up on our clinical experience and data of the literature [8–10]. We elaborated a clinical algorithm based on the patient's clinical history of the supposed allergic event to penicillin. The chronology of symptom onset was considered as the main item discriminating immediate and non-immediate reactions to penicillin [11]. Additional specific questions aimed to identify potentially serious reactions such as anaphylaxis, bullous eruption and severe exanthema. The duration of the reaction was also considered because, in our experience, duration of the reaction less than 24 h (immediate reactions) or more than 48 h (non-immediate reactions suggesting delayed-type hypersensitivity) were suggestive of penicillin allergy. Using a combination of these factors, we created three decision trees (Figure 1) to distinguish finally low and high risk patients.

Allergological work-up

All patients were included prospectively and were explored based on ENDA/EAACI recommendations [12]. Briefly, all patients underwent prick-tests, intradermal tests and/or patch tests using recommended dilutions and readings, with penicillin commercial solutions. The suspected penicillin was tested when the patient knew it or with amoxicillin when the suspected penicillin was unknown. Skin prick tests was performed with undiluted commercial solution of penicillins; amoxicillin (200 mg/ml), amoxicillin-clavulanic acid (200 mg/ml), cloxacillin (200 mg/ml), oxacillin

(200 mg/ml). Freshly prepared penicillins diluted with saline were used for intradermal skin tests with successive dilutions for amoxicillin, amoxicillin-clavulanic acid, cloxacillin and oxacillin (0.2, 2 and 20 mg/ml). Prick tests and intradermal tests were performed on the volar forearm and read after 20 min. Saline and chlorhydrate histamine (10 mg/ml, Stallergènes, France) were negative and positive controls, respectively. Prick test and intradermal tests were considered positive if the increase of the largest diameter was ≥ 3 mm and surrounded by flare [13]. When a delayed reaction was suspected, patch tests with amoxicillin trihydrate (10% pet.), dicloxacillin sodium (10% pet.) (Chemotechnique, Sweden) and freshly prepared patch test with amoxicillin-clavulanic acid (30% pet.) and oxacillin (30% pet.) were performed and read at day 2 and 3 or 4 according to the International Contact Dermatitis Research Group (ICDRG) recommendations as previously reported in drug hypersensitivity [14]. Reactions from + to +++ were considered as positive. When patch test was negative, prick and intradermal tests with readings at 20 min, day 2 and 3 or 4 were performed.

Penicillin oral provocation tests (OPT) were performed with the suspected penicillin when the skin test result remained negative. The challenge was performed during a 1-day hospital stay, with strict supervision of blood pressure, heart rate, and oxygen saturation before, during and up to 6 h after the challenge. It was a single-blind placebo-controlled oral challenge; first the placebo had been administered, followed successively by increasing doses of penicillin (amoxicillin, amoxicillin-clavulanic acid, cloxacillin and oxacillin) (250, 250 and 500 mg) with 2 h interval. Challenge was stopped when a clinical reaction occurred and was considered as positive if saturation decreased below 90% and/or if blood pressure decreased of more than 30% and/or a skin eruption (urticaria, angioedema or rash) occurred up to 7 days after the challenge.

Validation of the algorithm

To validate the algorithm, we prospectively included all patients who consulted four physicians in our allergy unit for suspected penicillin allergy between March 1 and November 30, 2012. Physicians classified patients by using the algorithm at the end of the anamnestic consultation and before performing allergy skin tests.

Statistical analysis

The specificity is defined as the probability that a non-allergic patient was classified at low risk of allergy

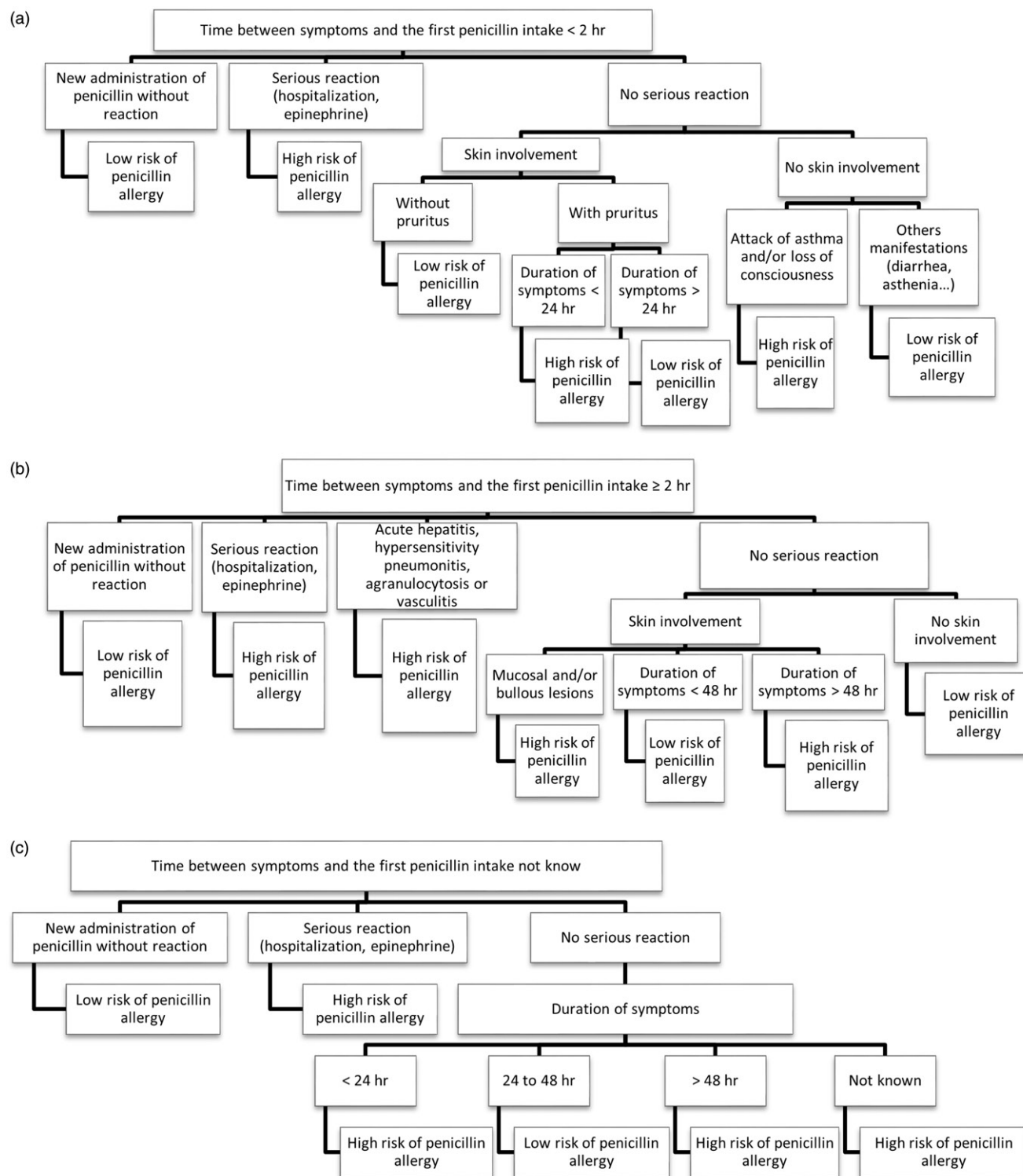


Figure 1. Clinical algorithm based on the patient's memory of the supposed allergic event to penicillin: three decision trees with 20 different situations resulting in two conclusions: low and high risk of penicillin allergy. (a) Suspected immediate hypersensitivity, (b) suspected delayed hypersensitivity and (c) not well-defined hypersensitivity reaction.

with the algorithm. The sensitivity is defined as the probability that an allergic patient was classified at high risk of allergy. The negative predictive value (NPV) is defined as the probability that a patient classified at low risk of allergy group was non-allergic, and

the positive predictive value (PPV) as the probability that a patient classified at high risk of allergy group was truly allergic to penicillin. The objective of the algorithm was to reach 100% sensitivity and NPV, to not misclassify patients with true penicillin allergy.

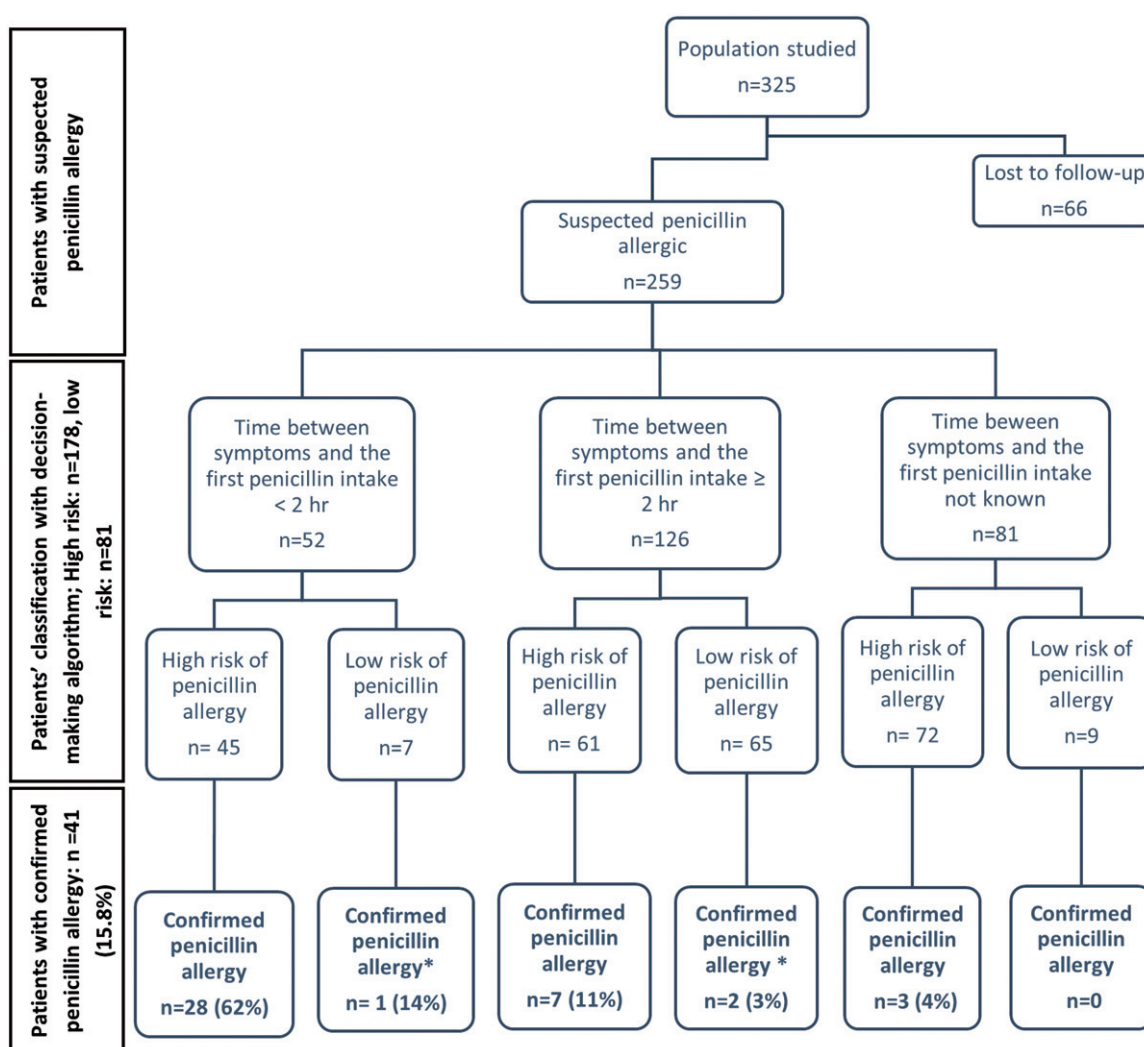


Figure 2. Flow of study population with classification of patients with penicillin allergy according to the decision-making algorithm and patients with confirmed penicillin allergy. Among 259 patients with suspected penicillin allergy, 41 had a confirmed allergy; 34 with positive penicillin skin test result and 7 with positive penicillin oral provocation tests results. *Three patients with confirmed penicillin allergy were misclassified with the algorithm.

Data were analyzed using STATA v11 for Windows (StataCorp, College Station, TX). Continuous variables were expressed as mean $\pm$ SD and categorical variables as number (%). Comparisons involved Student *t*-test for continuous variables and Fischer exact test for categorical variables. $p < .05$ was considered statistically significant. Sensitivity, specificity and positive and negative predictive values (PPV and NPV) of the algorithm were estimated. Finally, we compared the results of the decision-making algorithm with those of the allergological work-up.

Results

Population studied

We prospectively included 325 patients (mean age 47 ± 16 years, range 9–84; 80% women [$n = 208$])

referred to our institution for suspected penicillin allergy (Figure 2). Skin tests were negative in 291 patients (89.5%), of whom 66 (22.7%) did not perform the penicillin OPT and were considered lost to follow-up. Thus, a complete allergological work-up (i.e. penicillin skin test and OPT) was performed in 259 patients (79.7%), of whom 106 (41%) had a personal history of atopy.

According to clinical history, 52/259 completely explored patients (20.1%) reported a reaction occurring within 2 h of penicillin intake, and 126 (48.6%) reported a reaction occurring later. The chronology of the reaction was unknown in 81 cases (31.3%). The reaction was considered serious (i.e. hospitalization and/or use of epinephrine) for 27 patients (10.4%), of whom four reported non-immediate reactions and 23 immediate reactions. The allergological work-up was performed more than 10 years, 5–10 years, 1–5 years

Table 1. Delay between the reaction and the allergological work-up in high and low risk of penicillin allergy groups.

		High risk of penicillin allergy (<i>n</i> = 178)	Low risk of penicillin allergy (<i>n</i> = 81)	<i>p</i> value*
Delay between the reaction and the allergological work-up	<1 year	52 (29%)	11 (14%)	.004
	1–5 years	14 (8%)	14 (17%)	
	5–10 years	8 (5%)	8 (10%)	
	>10 years	104 (58%)	48 (59%)	

and less than 1 year after the reaction in respectively 152 (58.7%), 16 (6.2%), 28 (10.8%) and 63 (24.3%) patients (Table 1).

Results of allergological work-up

Overall, in 41/259 patients (15.8%) [95% CI: 11.5–20.3], we confirmed penicillin sensitization based on positive skin tests in 34 patients (83%) [95% CI: 7.1–13.8]; 27 positive immediate readings with prick tests (*n* = 10) and intradermal skin tests (*n* = 17), and 11 positive delayed readings with patch test (*n* = 1), prick tests (*n* = 4) and intradermal skin tests (*n* = 6). The total of positive skin tests was greater than 34 because four patients with delayed hypersensitivity reactions had both positive prick tests and intradermal skin tests.

In seven patients (17%) OPT confirmed penicillin allergy with 2 and 5 positive immediate and delayed challenge, respectively (Figure 2).

Of the 41 patients with confirmed penicillin allergy, 29 (71%), 9 (22%) and 3 (7%) had immediate-type, non-immediate-type hypersensitivity and unclassified reaction, respectively.

We found no significant difference between the patients with and without penicillin sensitization in terms of age, sex, atopy and/or chronic urticaria. Immediate and serious reactions were significantly more frequent in high risk of penicillin allergy group, based on algorithm classification, than in low risk of penicillin allergy group, in respectively 71 and 54% patients.

Comparison of allergological work-up and of the algorithm

Based on the algorithm's classification, three patients were considered at low risk of penicillin allergy although they were diagnosed allergic to penicillin based on positive immediate response in skin tests (*n* = 2) or OPT (*n* = 1). Patient 1 had clinical history of lip oedema and urticarial eruption few days after various antibiotics (i.e. spiramycin, josamycin, amoxicillin, amoxicillin-clavulanate acid and ofloxacin). The time lag between reaction and allergological work-up was 1 year, with negative skin test results (amoxicillin,

Table 2. Contingency table estimating the statistical performance of the decision-making algorithm.

Risk of penicillin allergy	No penicillin allergy	Confirmed penicillin allergy	Total
Low	78 <i>specificity: 35.8%, NPV: 96.3%</i>	3 <i>3.7% with true penicillin allergy misclassified (95% CI: 0.8–10.4)</i>	81
High	140	38 <i>sensitivity: 92.7%, PPV: 21.3%</i>	178
Total	218	41	259

PPV: positive predictive value; NPV: negative predictive value.

Italic font denotes the following: specificity: probability that a non-allergic patient was classified at low risk of allergy; sensitivity: probability that an allergic patient was classified at high risk of allergy; NPV: probability that a patient classified at low risk of allergy group was non-allergic; PPV: probability that a patient classified at high risk of allergy group was truly allergic.

amoxicillin-clavulanic acid with patch, prick and intradermal tests) at 20 min, days 2 and 4. A positive challenge occurred 5 min after the first dose of amoxicillin; with blood pressure decreased of more than 30%, skin rash, generalized pruritus and abdominal pain treated with epinephrine (0.3 ml). Two other patients had clinical history of hives and skin rash without pruritus, respectively, 10 days and 1 day after amoxicillin intake. The time lag between reaction and allergological work-up was 5 and 12 years, respectively. Patch tests with amoxicillin were negative, and intradermal tests with amoxicillin were positive at 20 min (2 and 20 mg/ml, respectively). Seventy-eight out of the 81 patients (96.3%) were well-classified in low risk group (Figure 2 and Table 2). Fifty-two of the 63 patients (82.5%) who consulted within 1 year after the suspected allergic reaction were classified at high risk of penicillin allergy, representing 29% (52/178) of the high-risk group and 11/63 (17.5%) were classified as low-risk patients, representing 13.6% (11/81) of the low-risk group (*p* = 0.004) (Table 1). We found no significant difference for patients consulting more than 10 years after the suspected allergic reaction.

The specificity and the sensitivity of algorithm were respectively 35.8% (95% CI: 29.4–42.5) and 92.7% (95% CI: 80.1–98.5) (Table 2). The NPV and the PPV were respectively 96.3% (95% CI: 89.6–99.2) and 21.3% (95% CI: 15.6–28.1). Finally, the probability that a patient with true penicillin allergy was misclassified was 3.7% (95% CI: 0.8–10.4) (Table 2).

Discussion

In this study, we aimed to design and validate a clinical decision-making algorithm for general practitioners

to help them assess the risk of allergy associated with a penicillin prescription. Overall, 15.8% of our patients had a confirmed penicillin allergy, which is consistent with results of other studies performed in adults and children with suspected drug allergy [1,15]. Diagnosis of penicillin allergy was based on responses in skin tests for 83% of patients and penicillin OPT for 17%, consistent with previous results [16]. Sixty-six patients (20.3%) in our study did not undergo OPT and were considered lost to follow-up. These patients did not differ from the completely explored patients in terms of epidemiologic criteria, clinical presentation and penicillin skin test results. In our allergology work-up, we did not perform prolonged oral provocation tests, that they followed patients for a possible delayed response. Few studies had reported prolonged provocation tests (3–7 days) with various proportion of positive hypersensitivities to betalactams (15.9–28.7%) [16–18].

Of the 178 patients classified in the high-risk group, 38 (21.3%) were diagnosed allergic to penicillin based on the results of the allergological work-up. Based on the algorithm 81 patients (96.3%) were classified at low risk of allergy. Diagnosis of penicillin allergy was ruled-out in 78 of these patients, based on negative responses in skin tests and OPT, but three patients were diagnosed allergic to penicillin, based on results of the allergological work-up. According to the anamnesis, two of them were misclassified as having a delayed reaction but showed positive immediate skin test results, for these two patients we cannot exclude totally a false positive skin tests, because as recommended in case of positive skin test, they were not challenged with OPT and it is still possible they were not clinically in high risk of allergy group and thus correctly positioned by algorithm. A third patient was classified as having a non-severe delayed reaction but, despite negative skin test results, experienced anaphylactic shock during the OPT.

These results are similar as reported by Hjortlund *et al.*; they included all 342 consecutive patients suspected of having betalactam allergy in a prospective way and compared the result of the algorithm with the results of diagnostic work up, including challenge test in patients with negative skin tests. Thirty-six patients were subclassified as immediate reactors, 235 patients as non-immediate reactors and 71 patients could not be subclassified with the chronology of the reaction. They reported 12 of the 19 patients with IgE-sensitization belonging to the group of non-immediate reactors and four patients in the group immediate reactors according to case history. Authors concluded that the data suggest case history is often insufficient

to discriminate between immediate reactors and non-immediate reactors and that finally 21.1% of patients in this study were unable to give a detailed case history regarding time interval between dosage and reaction [18].

The diagnostic value of positive skin tests had been reported in numerous studies, with various concentrations, methodology and population and using commercial penicillin solution or major and minor penicillin determinants not available in all countries. Due to the lack of standardization during long time, some studies cannot be compared. Prospective studies confirm that the skin test reactivity is lost over time in penicillin allergic patients [19,20]. The negative predictive value of penicillin skin testing is >95% or greater [21–23].

More than half of the patients (59%) consulted more than 10 years after their suspected allergic reaction, which questions the relevance and accuracy of the anamnesis in this group. However, this finding is not the only explanation for the misclassification of the three patients because allergy work-up was performed within 1 year of the initial reaction in one of them (anaphylactic shock during OPT), and 5 and 12 years later in the two other patients (immediate positive responses in skin tests).

The loss of memory of the immune response can be another explanation for the misclassification. Indeed, it has been showed that more than 50–100% of patients with penicillin allergy lose their skin sensitization and basophil activation test reactivity within 6 and 4 years of the initial allergy work-up, respectively [20,24]. Due to loss of memory of the immune response, any patient with suspected penicillin hypersensitivity should be evaluated by an allergist as soon as possible to avoid risk of false-negative allergy work-up due to a long-time interval between the suspected allergic reaction and the work-up [13].

Our findings are consistent with those of other studies showing that clinical history is not always a good predictor of penicillin allergy [25–27].

Recently, a mathematical model was developed based on retrospective medical history data of 466 patients reporting reactions to 696 active principles to predict the risk of drug allergy [28]. This model involved use of binary logistic regression to determine associations between clinical variables (age, sex, drug, time to reaction, number of doses and clinical presentation, without distinguishing between immediate and delayed reactions). However, the final diagnosis was not systematically confirmed with allergy explorations (skin tests, *in vitro* tests or drug provocation tests) and no valid conclusions can be drawn.

Some authors suggested a clinical guideline for prescribing antibiotics to patients with a history of penicillin or cephalosporin allergy; using a standardized two-steps test challenge; with administration of one-fourth of a pill for an oral medication followed by the full dose after 60 min of observation [29]. The adverse drug reaction rate during multistep challenges (more than two steps) was similar to two-step test challenge [30]. This clinical guideline was based on characterization of rashes and patient reactions were categorized [17].

In conclusion, the validity of our algorithm, both in terms of specificity and NPV, is good but not satisfactory because we aimed to reach 100% sensitivity and NPV. Three patients (3.7%) misclassified according to the algorithm had an immediate hypersensitivity reaction to penicillin, which could have led to severe or fatal anaphylaxis, as reported in 0.0015–0.002% of patients receiving penicillin [31,32]. This risk is too great to allow the use of this algorithm in general practice. However, it could be used in emergency situations in hospital settings, when alternate antibiotic cannot be used. Most patients with suspected penicillin allergy can be prescribed safely cephalosporins, except for patients reporting suspected allergic reactions to aminopenicillins (ampicillin, amoxicillin) in whom aminocephalosporins are contra-indicated (risk of cross-reactivity) until they have been explored [33]. Further additional studies are needed to improve the algorithm.

Disclosure statement

The authors report no conflicts of interest.

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