Urticaria : the 1-1-1 criterion for optimized risk stratification in β-lactam allergy delabeling

Original Article

Urticaria: The 1-1-1 Criterion for Optimized Risk Stratification in b-Lactam Allergy Delabeling

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What is already known about this topic? Low-risk patients can benefit from delabeling based on direct challenges. However, there is still no consensus about the risk status to assign to patients who have experienced an urticarial eruption associated with b-lactam treatment.

What does this article add to our knowledge? An urticarial eruption appearing within 1 hour after the first dose and with a maximal duration of 1 day is significantly more frequently observed in patients with a positive skin test/serum specific IgE assay.

How does this study impact current management guidelines? Patients who meet the 1-1-1 criterion are not eligible for a direct challenge, but should be referred for prior skin tests and serum specific IgE measurement.

BACKGROUND: A spurious label of b-lactam allergy compromises antibiotic stewardship. Delabeling protocols based on direct challenges (ie, not preceded by allergy tests) can be applied in low-risk patients.
OBJECTIVE: This study aims at determining the significance of the characteristics of urticaria in the risk stratification for delabeling.
METHODS: The characteristics of urticarial eruptions that had occurred during therapeutic courses with a b-lactam, namely the time interval between the exposure and onset, the dose (first or subsequent) after which urticaria appeared, and the duration of the eruption, were correlated to the results of a systematic allergy workup (skin tests, specific IgE measurements, and challenges). Data from 410 patients enrolled in 3 allergy centers (Rome and Troina, Italy, and Antwerp, Belgium) were analyzed. A multivariable logistic regression was performed, which included appearance within 1 hour after the first dose and regression within 1 day: a model that can be summarized as the "1-1-1" urticaria criterion.
RESULTS: An urticarial eruption that had appeared within 1 hour after the first dose and had regressed within 1 day was more frequently reported in the group with a positive allergy workup, with odds ratios of 17 (95% confidence interval [CI]: 9-31), 11 (95% CI: 6-20), and 48 (95% CI: 14-157), respectively ($P < .005$). The 1-1-1 criterion displayed a sensitivity and specificity of 85%, and a negative predictive value and a positive predictive value of 80% and 90%, respectively.
CONCLUSION: Patients with urticaria meeting the 1-1-1 criterion should be considered at high risk and referred for an allergy workup with skin testing and specific IgE measurement before challenging. (J Allergy Clin Immunol Pract 2021;9:3697-704)

Key words: Antibiotic stewardship; b-Lactams; Delabeling; Penicillin allergy; Risk assessment; Urticaria

Penicillins and cephalosporins constitute the predominant causes of drug-induced cutaneous reactions,[1,2] which can be classified as immediate and nonimmediate/delayed. The former occur within 6 hours of drug administration, though typically within 1 hour from the first dose of a new treatment course, whereas delayed reactions occur at any time from 1 hour after

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Abbreviations used

ANN- Artificial neural networks
AUC- Area under the curve
AX- Amoxicillin
AX/CLV- Amoxicillin þ clavulanic acid
BP-OL- Benzylpenicilloyl-octa-L-lysine
CI- Confidence interval
CLV- Clavulanic acid
DAIG- Drug allergy interest group
DC- Drug challenge
IDT- Intradermal test
LR- Logistic regression
MD- Minor determinant (sodium benzylpenilloate)
MDM- Minor determinant mixture
MPE- Maculopapular exanthema
NPV- Negative predictive value
OR- Odds ratio
PPL- Benzylpenicilloyl-poly-L-lysine
PPV- Positive predictive value
Se- Sensitivity
sIgE- Specific IgE
Sp- Specificity
SPT- Skin prick test
STs- Skin tests

drug administration to days or weeks thereafter.[3] In particular, penicillins (ie, penicillin G, penicillin V, amoxicillin [AX], and ampicillin) and cephalosporins were the drug classes accounting for approximately 37% and 4%, respectively, of 269,493 "rash/dermatitis" cases, as well as for 40% and 5%, respectively, of 150,450 "hives/urticaria" ones listed in a US-based electronic health-record analysis.[4] Both penicillins and cephalosporins can also cause anaphylaxis.[2,4,5] In a report by the Allergy Vigilance Network of the European registry of recorded drug-induced severe anaphylaxis, from 2002 to 2010, penicillins and cephalosporins caused 30.3% and 12.3% of the 333 cases, respectively.[6] Patients with a history of a b-lactam allergy have an increased risk of treatment failures and adverse events when treated with alternative, nonb-lactam antibiotics.[1] Moreover, a penicillin-allergy label is associated with higher risk for antibiotic resistance,[1,7] longer hospital stays, higher rates of readmission and surgical-site infections, and higher expenditure.[1,8] Importantly, a large majority of patients labeled as allergic to b-lactams tolerate penicillin and other b-lactams.[9] Because of the low prevalence of true b-lactam allergy and the disadvantages of alternative, nonb-lactam antibiotics, several studies have evaluated the safety and effectiveness of delabeling programs based on direct challenges (ie, not preceded by skin testing) in low-risk subjects.[10-15]

More than 80% of reported penicillin-induced reactions involve the skin, with urticaria as the most frequent presentation of an immediate hypersensitivity reaction.[8] However, the occurrence of urticaria during exposure to a b-lactam does not necessarily imply a causal link, indicating either an IgE-mediated or a nonIgE-mediated pathogenic mechanism, but can also result from the underlying infection.[1] To date, no consensus has been reached on the risk stratification of patients who have experienced urticaria associated with b-lactam therapy.[1,16] Some authors have classified patients reporting only cutaneous symptoms as medium risk.[1] However, referring to penicillin immediate reactions, they have considered "extensive" urticaria a severe reaction and "isolated" urticaria a nonsevere presentation. Other authors have defined urticaria and delayed maculopapular exanthema (MPE) as benign cutaneous reactions and classified subjects with such reactions as low-to-medium-risk.[16] In patients reporting either immediate or delayed "isolated" urticaria, the aforesaid authors have suggested a single-dose or graded-ingestion challenge or, alternatively, immediate-reading skin tests (STs) or delayed intradermal skin or patch testing followed, in case of a negative result, by a single-dose or graded-ingestion challenge.[16] Clearly, uncertainties and diverging opinions remain about the correct delabeling strategy in patients who have experienced urticarial eruptions associated with b-lactam treatments.

The main objective of this study is to analyze the characteristics of urticaria as the index reaction after exposure to a b-lactam and to correlate the clinical presentation with the outcomes of a systematic and standardized allergy workup including skin testing, a serum specific IgE (sIgE) assay, and a drug challenge (DC).

Ultimately, a better characterization of urticarial eruptions should advance the individual risk stratification and benefit guidance of diagnostic management.

METHODS

Patient population

We retrospectively analyzed the medical records of 410 patients who were referred to the Allergy Units of the Columbus Hospital, Rome, Italy; Oasi Research Institute-IRCCS, Troina, Italy (between January 2004 and June 2020 in both Italian units); and the Antwerp University Hospital, Belgium (between January 2012 and March 2020) because of urticarial eruptions associated with b-lactam treatments. Urticarial eruptions were confirmed by: (a) pictures in patients' dossiers/smartphones, (b) patients' recognition of pictures of skin eruptions included in a standardized questionnaire, or (c) clinical observation.

Inquiry about the characteristics of urticarial eruptions included:

1. Time interval between last administered dose and onset of eruption (<1 hour, >1 hour to <6 hours, >6 hours, or unknown). For the statistical analysis, the time interval was classified as ≤1 hour, >1 hour, or unknown;
2. Dose (first dose, subsequent one, or unknown) after which the urticarial eruption appeared; and
3. Duration of the eruption after stopping intake (≤1 day; >1 day, or unknown).

Note that patients unable to correctly report 1 or more of the 3 aforementioned characteristics of index urticarial eruptions were not included in the electronic databases of the 2 Italian centers.

Any reaction on re-exposure to the implicated b-lactam(s) during a subsequent course and clinical outcomes were also recorded. Anaphylactic reactions were diagnosed according to the clinical criteria proposed by Sampson et al.[17]

Before the allergy workup, all subjects received information about the possible risks of STs and DCs, and written informed consent was obtained from each patient or the representatives of those under 18 years of age. The protocol was approved by the respective institutional review boards.

Subjects with positive STs, sIgE assays, or DCs were registered as cases, whereas those subjects with a negative allergy workup represented the controls.

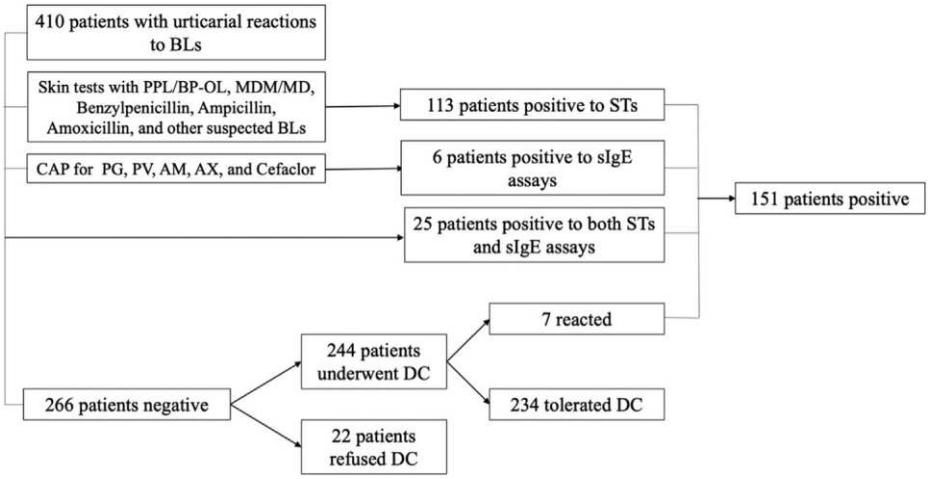

FIGURE 1. Flowchart of patient inclusion and results of allergy workup. *AM*, Ampicilloyl; *AX*, amoxicilloyl; *BLs*, b-lactams; *BP-OL*, benzylpenicilloyl-octa-L-lysine; *DC*, drug challenge; *MD*, minor determinant (sodium benzylpenilloate); *MDM*, minor determinant mixture (mixture of benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid); *PG*, penicilloyl G; *PPL*, benzylpenicilloyl-poly-L-lysine; *PV*, penicilloyl V; *sIgE*, specific IgE; *STs*, skin tests.

Allergy workup

Patients underwent a standardized allergy workup according to the European Academy of Allergy and Clinical Immunology drug allergy interest group (DAIG) guidelines including STs, sIgE assays, and DCs.[18-20]

Skin tests. STs were performed with benzylpenicillin, benzylpenicillin reagents, and any other suspected b-lactams. Benzylpenicillin reagents comprised benzylpenicilloyl-poly-L-lysine (PPL; Allergopharma, Reinbeck, Germany), minor determinant mixture (MDM, benzylpenicillin and sodium benzylpenicilloate; Allergopharma), and benzylpenicillin itself. The final concentrations were, respectively, 3×10^{-5} mol/L, 2×10^{-2} mol/L, and 10,000 IU/mL. Because Allergopharma ceased production of penicillin reagents, from July 2005, those produced by Diater (DAP, Leganés, Spain) were used: PPL (final concentration: 1.07×10^{-2} mol/L) and MDM (benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid; final concentration: 1.5 mol/L). From May 2011, the composition of the DAP changed: benzylpenicilloyl-octa-L-lysine (BP-OL) replaced PPL and sodium benzylpenilloate (minor determinant [MD]) replaced the MDM. The final concentrations of BP-OL and MD were 8.64×10^{-5} mol/L (ie, undiluted) and 1.5×10^{-3} mol/L (ie, undiluted), respectively. STs with AX, as well as with other suspected penicillins and suspected cephalosporins, were performed at concentrations that had proved to be nonirritating.[20] For AX and other penicillins, a maximum concentration of 20 mg/mL was used. From March 2010, the combination AX b clavulanic acid (AX/CLV) at concentrations of 20 and 4 mg/mL, respectively, was also used in subjects who had reacted to the above combination and were negative to STs with AX. From January 2018, CLV (Diater), at concentrations of 1 and 20 mg/mL, was used in such subjects to replace AX/CLV. Suspected cephalosporins, diluted with 0.9% NaCl no more than 2 hours before use, were tested at a maximum concentration of 2 mg/mL. From June 2013, all cephalosporins except cefepime were tested at a maximum concentration of 20 mg/mL.[21-23]

Note that STs with PPL/BP-OL, MDM/MD, ampicillin, and CLV were not carried out in the Belgian allergy unit due to the unavailability of these reagents. All of the above reagents were initially tested on volar forearm skin by the prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When prick tests were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin, using a disposable 1 mL syringe. For intradermal tests (IDTs), immediate and delayed readings were performed after 20 minutes and 48 hours, respectively. In immediate readings, results were considered positive when there was an increase of larger than 3 mm in the initial wheal diameter surrounded by erythema 2 mm more than control one. Delayed IDT readings were considered positive when an erythematous, raised, and infiltrative lesion or an eczematous one with a diameter larger than 5 mm was observed at the injection site after 48 to 72 hours.[20,24] Positive controls for skin prick tests (SPTs) and IDTs were done with histamine. As a negative control for SPTs and IDTs, 0.9% NaCl was used.

In vitro tests

We performed assays for serum total and sIgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor with ImmunoCAP (Phadia, Uppsala, Sweden, now Thermo Fisher Scientific) in all subjects with urticarial reactions that had occurred within 1 hour after the last penicillin or cefaclor administration and in all those with anaphylactic reactions. A value of 0.35 kUA/L or greater was considered positive.

Drug challenges. A graded DC with the suspected b-lactam was proposed to all patients with negative STs and sIgE assays. DCs were performed according to the European Academy of Allergy and Clinical Immunology DAIG guidelines.[18,19,24] We used a 3-step challenge protocol. In the first step, we administered an initial dose of one-hundredth of the therapeutic one. In cases with negative results, 1 hour later we administered a dose of one-tenth and, if the result was again negative, after another hour a full therapeutic dose. Subjects reporting hypersensitivity reactions to AX/CLV underwent challenges with AX and, in case of negative results, a further challenge with AX/CLV. For intramuscular challenges, doses of one-hundredth and one-tenth were injected in deltoid muscles and full

TABLE I. Characteristics of the 410 subjects and results of the allergy workup

Characteristic	Italian cohort (n [296)	Belgian cohort (n [114)
Age, median (IQR)	42 (29)	40 (32)
Adults, n (%)	270 (91.2)	106 (93)
Female, n (%)	210 (70.9)	80 (70.2)
Patients with a second reaction during subsequent course, n (%)	59 (19.9) [23 anaphylaxis]	5 (4.4) [2 anaphylaxis]
Patients with a third reaction during subsequent course, n (%)	4 (1.3) [1 anaphylaxis]	e
Time, symptom onset, n (%)		
<1 h	136 (45.9)	44 (38.6)
>1 to <6 h	56 (18.9)	10 (8.8)
>6 h	104 (35.1)	20 (17.5)
Unknown	e	40 (35.1)
Culprit dose, n (%)		
First dose	148 (50)	36 (31.6)
Subsequent dose	148 (50)	34 (29.8)
Unknown	e	44 (38.6)
Duration of symptoms, n (%)		
<1 d	207 (69.9)	42 (36.8)
>1 d	89 (30.1)	35 (30.7)
Unknown	e	37 (32.5)
Time interval*, median (IQR)	11 (46)	6 (51)
Positive skin tests, n (%)		
PPL/BP-OL	20 (6.8)	NP
MDM/MD	15 (5.1)	NP
Benzylpenicillin	23 (7.8)	3 (2.6)
Ampicillin	48 (16.2)	NP
Amoxicillin	50 (16.9)	24 (21.1)
Other suspected b-lactams	93 (31.4)	37 (32.5)
Specific IgE [2:0.35 kUA/L], n (%)		
Penicilloyl G	24 (8.1)	6 (5.3)
Penicilloyl V	22 (7.4)	7 (6.1)
Ampicilloyl	19 (6.4)	7 (6.1)
Amoxicilloyl	13 (4.4)	3 (2.6)
Cefaclor	5 (1.7)	1 (0.9)
Drug challenge, n (%)		
NP because of positive allergy tests	107 (36.1)	37 (32.5)
Refused	22 (7.4)	e
Negative	160 (54.1)	77 (67.5)
Positive	7† (2.4)	e

BP-OL, Benzylpenicilloyl-octa-L-lysine; *IQR*, interquartile range; *MD*, minor determinant (sodium benzylpenilloate); *MDM*, minor determinant mixture; *NP*, not performed; *PPL*, benzylpenicilloyl-poly-L-lysine.

*Time (months) elapsed between the last urticarial eruption after b-lactam exposure and the allergy workup.

†Six of 7 patients reported a 1-1-1 urticaria.

therapeutic doses in the gluteus. Each patient was carefully monitored and complete equipment for cardiopulmonary resuscitation was immediately available.

Statistics

Univariable logistic regression (LR) models were used to evaluate the odds ratio (OR) for the 3 characteristics of urticarial eruptions in relation to a positive allergy workup. Subsequently, a multifactorial LR was built, which included 1 indicator variable for each of the 3 urticaria characteristics, namely, onset, dose, and duration, required to meet the 1-1-1 criterion. Sensitivity (Se), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV), accuracy, and area under the curve (AUC) were determined and the corresponding 95% confidence interval (CI) was calculated. Results were validated by 10-fold cross-validation. Mosaic plots were constructed to visualize the results. Statistical analysis was performed by JMP Pro 15.0 Software (SAS, Cary, NC). Results were considered significant when $P < .05$. We specified the number of missing data in the Results section.

RESULTS

Patients' characteristics and results of allergy workup

Figure 1 displays a flowchart of patients included, and Table I shows the demographics, clinical features, and results of allergy testing. Our 410 patients reported 482 suspected reactions after exposure to b-lactams; 342 subjects had had a single urticarial eruption, whereas 64 had experienced a second reaction and 4 a third because of re-exposure to the culprit b-lactams or cross-

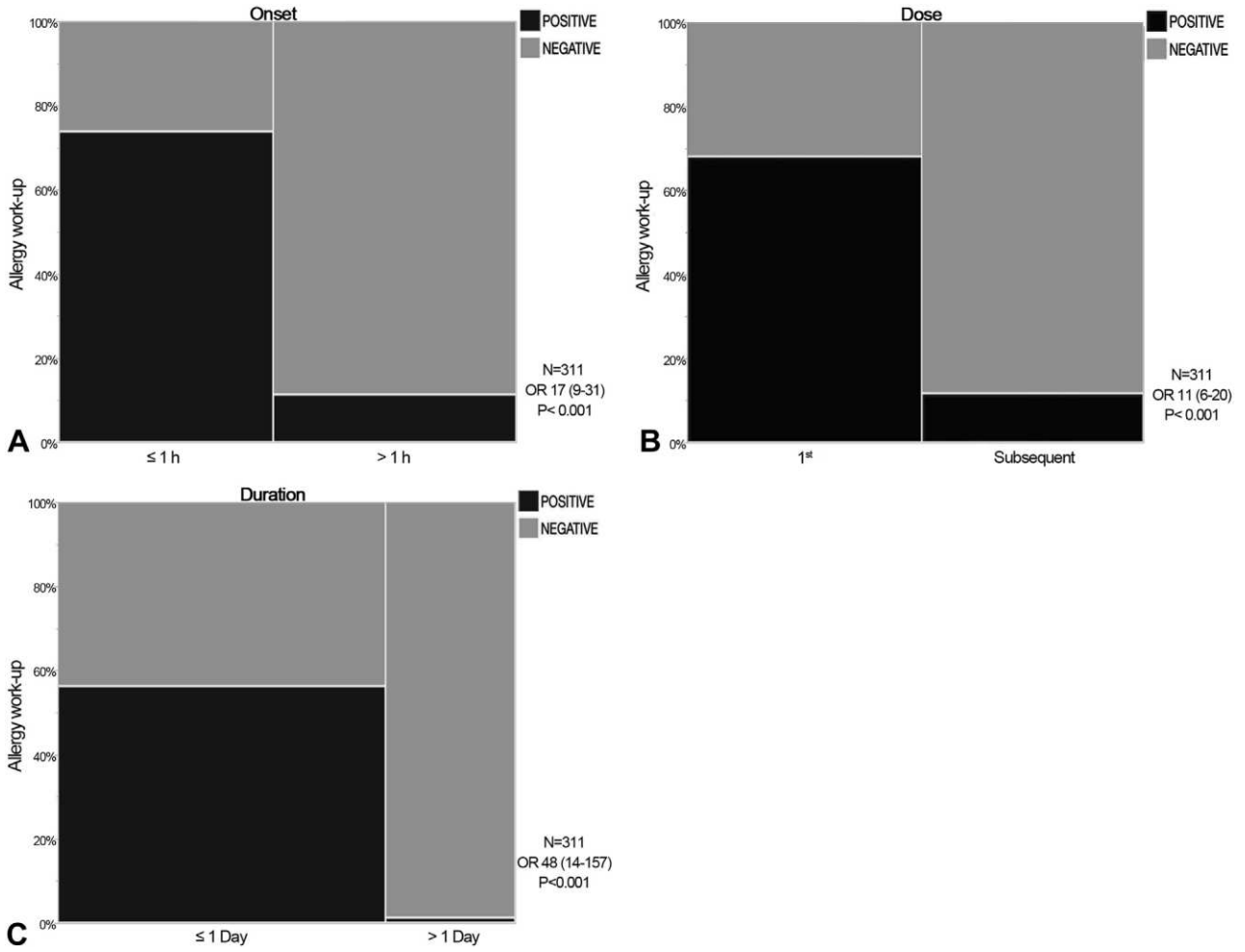

FIGURE 2. Univariable analysis. Mosaic plots urticarial characteristics: (A) onset, (B) dose, and (C) duration. Analysis is restricted to patients who were able to recall all 3 of the urticaria characteristics and who, in case of negative allergy test, underwent a drug challenge. *OR*, odds ratio.

reacting ones during subsequent courses. In all, 68 of 410 (16.5%) patients reported reactions during subsequent courses; 26 of them (6.3%) had had anaphylactic reactions.

Univariable analysis showed that urticaria with an onset within 1 hour (OR: 17, 95% CI: 9-31, P < .001) after the first dose (OR: 11, 95% CI: 6-20, P < .001), and with a maximal duration of 1 day (OR: 48, 95% CI: 14-157, P < .001) was significantly associated with positive allergy workup results (Figure 2, A-C). Among patients unable to recall at least 2 of the 2 other relevant urticarial characteristics—dose and onset—(n ¼ 7), a duration of at most 1 day was more frequent in those with positive tests (OR: 29, 95% CI: 6-141, P < .001).

Figure 3 shows the characteristics of urticarial eruptions in relation to the result of the allergy workup. Urticaria fulfilling the 1-1-1 criterion (appearance within 1 hour after the first dose and regression within 1 day) was reported by 122 of the 151 (80%) subjects found positive to allergy testing. Of these 122 subjects, 86 were positive only to STs, 6 only to sIgE assays, 23 to both tests, and 7 to challenges. Note that the time interval (months, median [interquartile range]) between the index reaction and testing in patients with positive and those with negative test results (4 [15] vs 7 [21]) was not significantly different. Multivariable analysis, covering 300 subjects, confirmed that onset within 1 hour, first dose, and duration of 1 day or less were independent predictors of a positive allergy workup. When the 1-1-1 criterion is applied to predict a positive allergy workup, it displays an Se, Sp, NPV, and PPV of 85% (95% CI: 74-89), 85% (95% CI: 80-94), 80% (95% CI: 76-89), and 90% (95% CI: 80-94), respectively, with an accuracy of 85% (95% CI: 80-89) and AUC of 0.9 (95% CI: 0.85-0.98). A 10-fold cross-validation confirmed the performance of this model.

Among the 68 patients with a reaction during subsequent courses, 34 of the 42 (80%) patients who had had urticaria and 25 of the 26 (96%) who had experienced anaphylaxis reported 1-1-1 urticaria. Regarding these 25 subjects, the administration route was oral in 23 and intravenous in 2. It had been the same route of the index reaction for all the subjects except one who, after an oral therapeutic course, received a subsequent intravenous course.

Moreover, 23 patients who had an urticarial eruption after exposure to a b-lactam reported a history of chronic spontaneous urticaria. Among them, only the 2 patients with a 1-1-1 urticarial

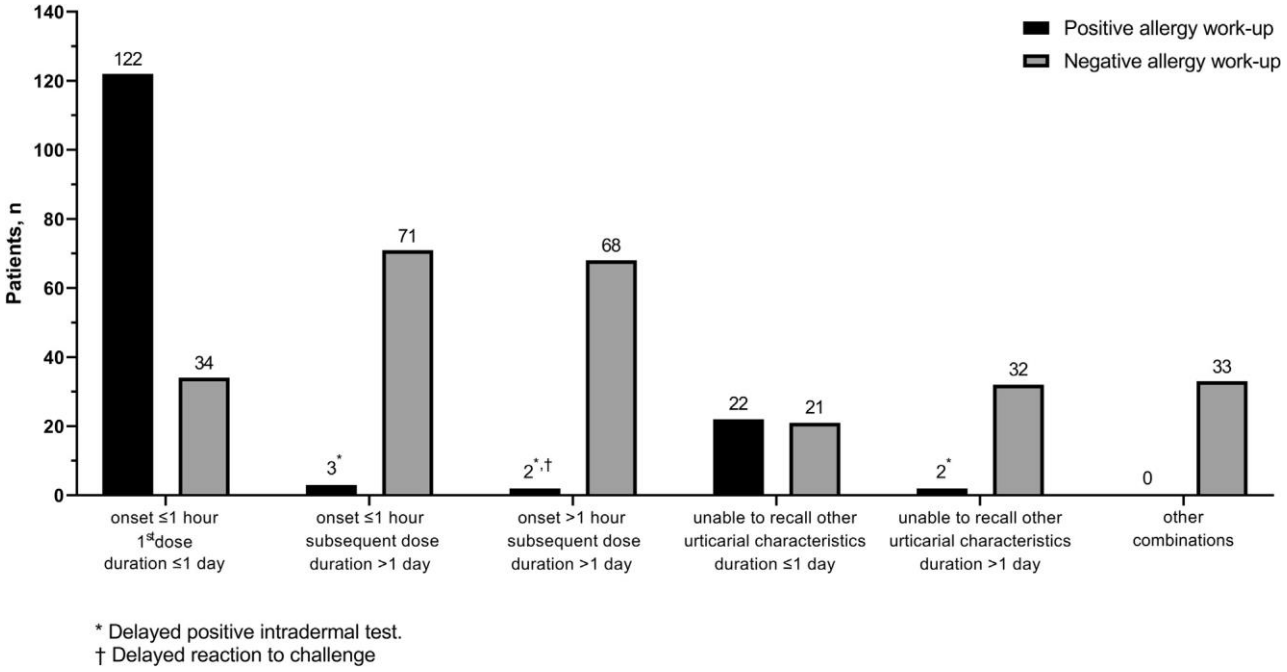

FIGURE 3. Characteristics of urticarial eruptions in patients with positive (n ¼ 151) and negative (n ¼ 259) allergy workup. Twenty-two patients refused the drug challenge. Multivariable analysis showed that the 1-1-1 criterion has sensitivity, specificity, negative predictive value, and positive predictive value of 85%, 85%, 80%, and 90%, respectively.

eruption resulted positive in the allergy workup. The 21 subjects with a negative allergy workup reported an urticarial eruption with characteristics other than 1-1-1 as their index reaction.

Penicillins, mostly AX, were the implicated b-lactams in 92 patients, cephalosporins in 48, and both in 2 (Figure 4). CLV was the culprit b-lactam in 2 subjects who had reacted to AX/CLV by experiencing a 1-1-1 urticaria. They displayed negative STs to AX and positive ones to the combination AX/CLV at concentrations of 20 and 4 mg/mL, respectively. Both subjects tolerated AX challenges.

DISCUSSION

A false b-lactam allergy label is a major problem because of its negative clinical and financial impact.[1,7,9,16] Conversely, there is unambiguous evidence that patients who have been correctly delabeled, due to the availability of allergy delabeling programs, have better clinical outcomes. Today, 5% to 15% of the population in developed countries reports a "penicillin allergy."[1] Nevertheless, in more than 95% of them, penicillin can be safely administered after an appropriate diagnostic evaluation.[16] However, a complete allergy workup with STs, sIgE assays, and DCs is a time-consuming, labor-intensive, and expensive approach. Furthermore, the limited number of specialized allergy centers cannot ensure an adequate response to the high demand for delabeling. The reference standard to confirm b-lactam tolerance is a controlled DC with a full therapeutic dose. However, as DCs remain a potentially harmful procedure, a correct individual risk assessment is mandatory to avoid complications. Direct b-lactam challenges are recommendable exclusively in low-risk patients.

To date, there is no broad consensus on the risk stratification of subjects reporting urticarial eruptions associated with b-lactam therapy. Specifically, some authors include immediate "extensive" urticaria among severe reactions and immediate "isolated" urticaria among nonsevere ones,[1,7] whereas others define urticaria as a benign cutaneous reaction (like delayed MPE), regardless of the time lapse (ie, immediate or delayed).[16] Consequently, in this clinical context, delabeling strategies can entail the risk of harmful choices, such as performing a direct DC or administration as a rule for patients with urticaria as their index reaction. Our results show that the time of onset of urticaria, the dose after which it appears during a therapeutic course, and its duration after stopping the latter are of the outmost importance for the individual risk stratification. In particular, patients with a positive allergy workup report significantly more frequently an urticarial eruption with onset within 1 hour after the first dose and regression within 1 day.

Previous studies have evaluated the influence of clinical histories and the characteristics of skin rash on risk stratification.

A retrospective study in 1092 patients with histories of b-lactam allergy identified a "low-risk" cohort that had all of the following features: "no history of anaphylaxis to b-lactams," "a reaction to a b-lactam more than 1 year before referral," and "unknown name of the index drug." The NPV of the history at presentation for a type I (ie, IgE-mediated) hypersensitivity reaction with the 3 characteristics of the "low-risk" cohort was 98.4%, which was similar to the NPV of 98.9% of skin testing for a type I hypersensitivity reaction in the whole cohort.[25] A multicenter Australian study analyzed the testing strategy (skin testing and/or oral penicillin challenge) and outcomes in 477 patients with a history of penicillin allergy.[26] A history of benign, immediate, or delayed rash (ie, urticarial and maculopapular

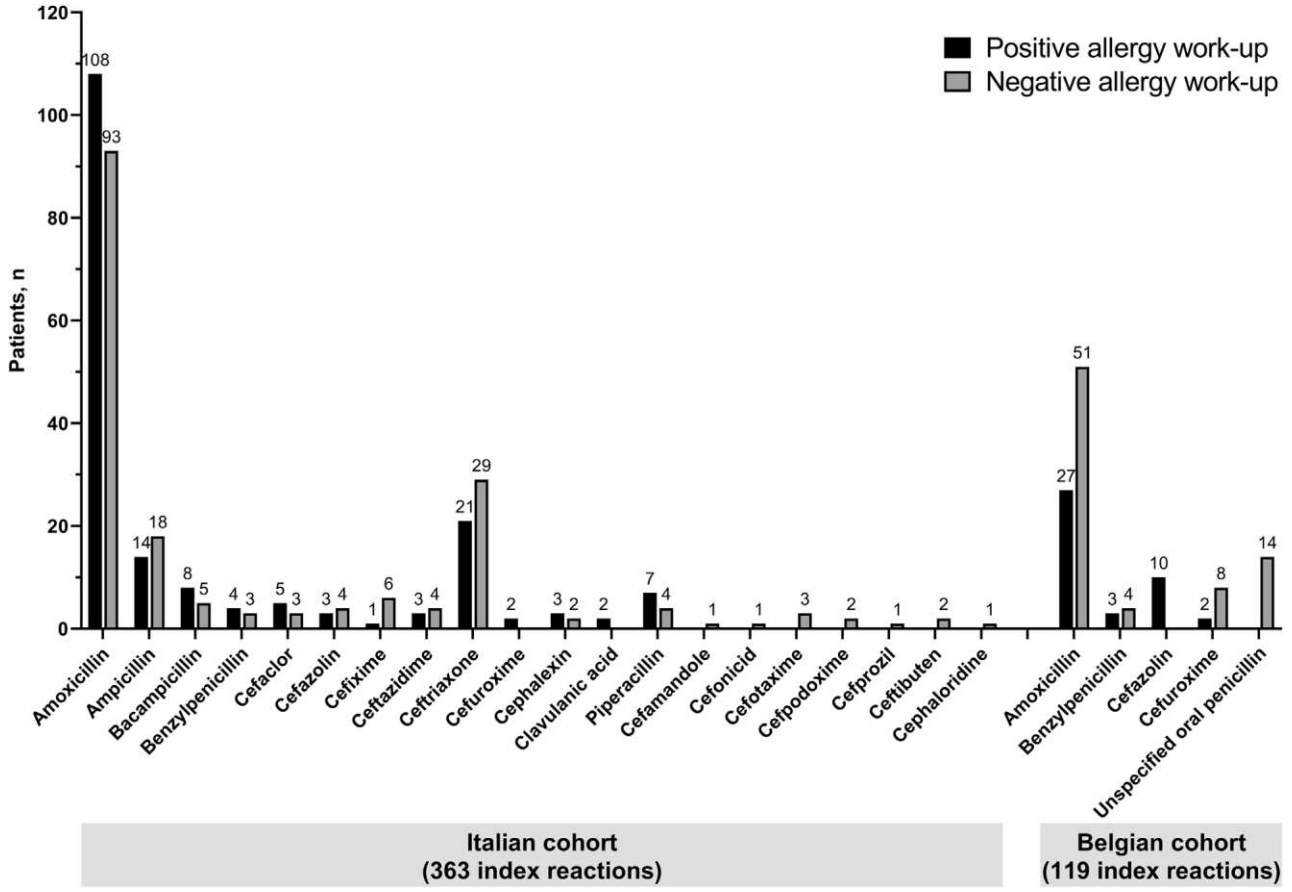

FIGURE 4. b-Lactams implicated in urticarial eruptions and anaphylactic reactions according to the results of the allergy workup. A total of 482 index reactions were reported. Allergy workup included skin test, specific IgE assay, and drug challenge. Twenty-two patients refused drug challenges.

rashes without angioedema, mucosal ulceration, or systemic involvement) more than 1 year before evaluation was the optimal low-risk definition. Of 244 patients with such a history, 237 (97.1%) tolerated a 1- or 2-dose penicillin challenge. None of the patients who reacted to DCs experienced anaphylaxis.[26] In another study,[27] subjects reporting only a "benign" rash (ie, urticaria, exanthematous rash, angioedema) more than 1 hour after the first dose or during a course of therapy were included among the 143 subjects classified as low-risk, 93.7% of whom tolerated penicillin challenges.

In the aforementioned studies,[11,12,14,15] the population consisted mainly of children, and "benign rashes" in most cases exhibited the features of an MPE. Based on these reports, a recent European position paper states that direct DCs can be performed in children with a mild MPE but not in adults with nonimmediate reactions other than palmar exfoliative exanthema.[20] Furthermore, according to the above-mentioned position paper,[20] patients who experienced immediate urticarial reactions to b-lactams, especially within the first hour after exposure, are classified as high-risk and should not undergo direct DCs. The results of our study endorse this recommendation and also highlight the importance of 2 other clinical characteristics of the urticarial eruptions, namely the dose (ie, the first or a subsequent one) and the duration of the eruption. Approximately 80% of subjects found to be positive to allergy testing reported urticaria that appeared within 1 hour after the first dose and disappeared within 1 day. Urticaria after exposure to a b-lactam that meets the 1-1-1 criterion (appearance within 1 hour after the first dose and regression within 1 day) is highly predictive of positive allergy testing. Furthermore, a duration of at most 1 day was significantly more frequent in patients with a positive allergy workup, even in those unable to recollect correctly at least 1 of the 2 other relevant urticaria characteristics.

Our data show that approximately 16% of the patients who had experienced urticaria as an index reaction suffered from a new reaction because of b-lactam re-exposure during additional courses, and around 6% even experienced anaphylaxis. Note that 25 of the 26 subjects who had experienced anaphylaxis on re-exposure to the responsible b-lactams or cross-reacting ones during subsequent therapeutic courses reported a 1-1-1 urticaria as their index reaction.

Furthermore, 14 of 15 patients in the Italian cohort and 7 of 8 in the Antwerp cohort who suffered from chronic spontaneous urticaria had a negative allergy workup, including DCs. Again, the 1-1-1 urticarial eruption was reported only in the 2 patients with a positive allergy workup.

It should be noted that there was no significant difference between subjects with positive and those with negative allergy

testing with regard to the time interval between the last β-lactam reaction and testing, with a median of 4 and 7 months, respectively. This finding suggests that in patients with an urticarial eruption, such time interval has limited influence on risk stratification.

Another important factor when considering delabeling strategies is the age of the patient. The patients included in this study are mostly adults. A subgroup analysis for young children was not sufficiently powered. Therefore, whether our findings apply to children, in whom the main cause of acute urticaria is an infection,[28] remains to be evaluated in further studies.

Recently, artificial neural networks (ANN) have been proposed as tools for predicting clinical reactivity with performances higher than LR, because ANN can better elaborate nonlinear relationships than LR.[29] However, to date both ANN and LR models entail a risk of misclassification, especially in patients who have had an urticaria as an index reaction.[29,30] Because such patients are those most frequently encountered in clinical practice and there is no reliable instrument to predict allergy, the most appropriate way for optimal management is to identify the high-risk urticaria subjects, who should be referred to an allergist.

Although based on a retrospective study, our model offers a prompt and reliable instrument, easily accessible by the medical community, for risk stratification of patients with urticaria as index reaction.

Our data indicate that urticarial eruptions meeting the 1-1-1 criterion should not be classified as benign manifestations. Patients who have experienced such urticarial eruptions should be considered at high risk and referred for skin testing as the initial diagnostic method.

In conclusion, our clinical scoring of urticaria constitutes a valid point-of-care method to improve antibiotic stewardship programs, as it enables doctors to discriminate between low- and high-risk patients among those who have experienced urticarial eruptions associated with β-lactam treatments. This model can help in optimizing the balance among accuracy, safety, cost, time, labor, and patients' comfort in delabeling strategies. Furthermore, implementation of this scoring system by the nonallergist community can reduce the burden related to the overlabeling of β-lactam allergy.

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