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Cross-reactivity in beta-lactams after a non-immediate cutaneous adverse reaction: experience of a reference center for toxic bullous diseases and severe cutaneous adverse reactions

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Abstract

Background

Cross-reactivity among beta-lactam antibiotics (BL) is essentially reported in immediate hypersensitivity.

Objectives

To evaluate cross-reactivity beyond BLs in patients with non-immediate cutaneous adverse drug reaction (non-immediate CADR) managed in a dermatology reference center of toxic bullous and severe CADR.

Patients/Materials/Methods

We conducted a retrospective single center study in consecutive patients consulting between 2010 and 2018 with an active BL-suspected non-immediate CADR and explored by cutaneous tests [patch tests (PT) and intradermic tests (P-IDR)] for at least three penicillin's subclasses and amino- and nonamino-cephalosporins (at least one aminoccephalosporin). Cross-reactivity among subclasses was investigated for patients with positive tests.

Results

We included 56 patients, among whom 46 amoxicillin-suspected were and 7 cephalosporin-suspected. Twenty-nine had severe CADR and 27 had non-immediate maculo-papular exanthema (MPE). Twenty-two had positive tests (18 for AS and 4 for CS). Among the 18 positive amoxicillin-suspected, 10 (55.6%) showed cross-reactivity with one or more other BL: 9 (50%) with another penicillin and 3 (16.5%) with a non-aminocephalosporin. No amoxicillin- or cephalosporin-suspected patient showed cross-reactivity with aztreonam or carbapenems. P-IDR showed cross-reactivity only once.

Conclusion

After a suspected BL-induced non-immediate CADR, a large allergologic exploration is needed to confirm the diagnosis and evaluate cross-reactivity. In our population including cases of severe

CADRs and MPE with late delay of onset, cross reactivity was frequent and PT were sufficient to this purpose. The frequent cross-reactivity among penicillins encourages stopping this whole family and to test cephalosporins, aztreonam and carbapenems for which cross-allergies are rarer.

Introduction

Beta-lactam (BL) antibiotics are a first-line treatment for many common infections but are often implicated in cutaneous adverse drug reactions (CADRs), even severe ones [epidermal necrolysis, including Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and generalized fixed drug eruption (FDE)]¹⁻⁶. Without a proper allergologic exploration, empiric stopping of all BL antibiotics is suggested, which may lead to prescribing less effective, more expensive, poorly tolerated or with wider antibacterial spectrum molecules⁷ with potentially increased adverse events⁸⁻¹⁰.

Many studies have been published on cross-reactivity in patients with IgE-mediated immediate hypersensitivity to BL, for which intradermic tests have high sensitivity and specificity⁴. Non-immediate CADRs have been defined as onset occurring more than 1 hr after drug intake, and mostly more than 1 day for MPE¹¹⁻¹³. Non-immediate CADRs include then a wide spectrum of CADRs, from late urticaria occurring a few hours after drug intake to maculopapular exanthema (MPE) and severe CADRs. However, published studies of BL-induced non-immediate CADRs included heterogeneous patients and mainly “erythema” “oedema”, urticaria and MPE without data on the delay of onset¹⁴⁻²⁰. In contrast, few studies included patients with precise or severe phenotypes of late CADRs²¹⁻²³.

Cross-reactivity among BL is usually explored by skin tests, sometimes followed by rechallenges²⁶. However, lack of consensus and standardization remains on how to explore different types of non-immediate CADRs²⁴. Patch tests (PTs) have been long recommended to explore non-immediate CADRs²⁵. They are followed, since more recently, by delayed readings of prick and intradermal tests (P-IDRs) in case of negative results and only for non-severe cases, but their added value in non-immediate CADRs induced by BL remains under-reported.

Our reference center for toxic bullous diseases and severe drug reactions benefits from a 24/7 dermatology emergency unit, in which we receive patients with all types of active CADRs. We also have an allergology consultation dedicated to exploration of non-immediate CADRs (immediate reactions are tested in another department). The aim of our study was to investigate the value of skin tests for cross-reactivity among BLs in this population of BL-suspected non-immediate CADRs.

Methods

Study population

This retrospective monocenter study was conducted in our dermatology department, which is as mentioned above a reference center for toxic bullous diseases and other severe CADR. Patients were selected from the allergology database.

The inclusion criteria were patients older than 18 years having consulted in our dermatological emergency unit from 2010 to 2018 for a non-immediate CADR with a suspected BL drug, alone or with other culprit drugs and explored by skin tests with at least three penicillin subclasses (A, G or V, and dicloxacillin), cephalexin (amino-cephalosporin of first-generation that share a similar aminobenzyle R1-side-chain with amoxicillin¹⁵) and one or more non-amino-cephalosporin. Other BLs, including aztreonam and carbapenems, may have been tested and were recorded.

The exclusion criteria were doubtful diagnoses or charts with missing data, cases attributed to a drug other than a BL by positive tests or a negative provocation test with the suspected BL drug.

The following data were obtained from medical charts: age, sex, type of non-immediate CADR (according to European Academy of Allergy and Clinical Immunology criteria¹²), time between first intake and onset of the eruption, time between the non-immediate CADR and skin tests, type of skin tests performed and results.

PTs and P-IDR materials

In our department, non-immediate CADR were explored by PT only up to the end of 2013. From January 2014, for all BL subclasses remaining negative in PT, further investigations by delayed readings of P-IDR was performed as routine except for cases of DRESS, SJS/TEN and FDE.

PTs were performed according to the guidelines diluted at 10% of the active ingredient or 30% of the finished product²⁷. When available, BL reagents were provided by Chemotechnique Diagnostics (Vellinge, Sweden) in ready-to-use syringes (amoxicillin, cloxacillin, dicloxacillin, G-penicillin, cephalexin, cefradin, cefotaxime). If they were not, reagents were prepared by our hospital pharmacy (V-penicillin, cefazolin, ceftriaxone, ceftazidime, cefepime, cefuroxime, cefoxitine, meropenem, imipenem, aztreonam).

PTs were applied on the upper back for 2 days, by using Q or IQ chambers (Chemotechnique Diagnostics) at least 6 weeks after the disappearance of the CADR (6 months for DRESS)^{27,28}. For FDE, PTs were applied *in loco* and on the upper back. The tests were read on day 2 and day 4.

For drugs with a negative PT result, P-IDRs were performed. Prick tests were performed with the therapeutic dilution of the drug (named “pure concentration”) for parenteral available drugs or with the PT preparation for drugs not available in injectable form. For IDRs, each solution was diluted sequentially in physiological saline (0.9% NaCl). In accordance with guidelines, 0.03 mL of solution at dilution 1/1000 to 1/10 of the pure drug was injected on the extensor surface of the arm²⁹. Late reading of P-IDR was considered positive if an infiltrated erythematous reaction was observed on day 3³⁰. Patients with DRESS and bullous drug reactions (FDE, SJS/TEN) were explored, as recommended, only by PTs.

Detailed sources and concentrations of BL reagents for PTs and P-IDRs are provided in supplemental data.

A patient was considered allergic to a BL drug if one of the tests (PT or P-IDR) was positive to a BL, either the suspected one or another.

P-IDR were considered useful if they permitted to identify an allergy or a cross-reactivity for a drug negative in PT.

Cross-reactivity was assessed only for patients with a positive BL drug test and defined by positivity to at least one BL drug of another subclass than the suspected one.

Objectives

The objective was to investigate by skin tests the rate of patients with cross-reactivity among BL subclasses.

Statistical analysis

Data were analyzed by using Microsoft Excel and RStudio v1.1.423. Quantitative data are described with median (interquartile range [IQR]) and were compared by Wilcoxon test. Categorical data are

described with number (%) and 95% confidence intervals (CIs) and were compared by chi-square test. $P < 0.05$ was considered statistically significant.

Ethics

The study was approved by the local institutional review board on 2018/07/12.

Results

Patients characteristics

Among 114 patients selected in the allergologic database, 58 were excluded because of doubtful diagnosis of CADR, another identified culprit drug (by positive test result or rechallenge) or patients not seen with active CADR. We included 56 patients in the final analysis (28 males, median age 59 [IQR 40–66] years) (Table 1).

We included 29 (51.8%) severe CADR [23 AGEP, 3 DRESS, 1 SJS, and 2 FDE] and 27 MPE (Table 1). All MPE were non-immediate CADR, with a median time to onset of 8 days in absence of previous allergy (IQR 4–11, range 2–33).

All patients had PTs and 22 also had P-IDR for the BL drugs with negative PTs. The median time between the CADR and the first day of allergologic exploration, available for 42 patients, was 124 [IQR 83–181] days. This time interval did not differ among patients with positive or negative skin tests (123 vs 126 days, $p = 0.58$).

Amoxicillin was suspected in 46 (82.1%) patients, cloxacillin or dicloxacillin in 3 (5.4%), non-aminoccephalosporin in 7 (12.5%) and aztreonam in 1 (1.8%) (1 patient had both amoxicillin and cefpodoxime suspected). No case of aminoccephalosporin-suspected allergy was recorded.

Table 1

Results of skin tests and cross reactivity (Table 2)

Skin tests were positive in 22/56 patients (39.3%, CI [26.5–52.1]): suspected drugs were amoxicillin in 18 patients, cloxacillin in 1 patient and non-aminocephalosporins in 4 patients. One patient with amoxicillin and cephalosporin suspected had positive tests to both. It should be noted that 2 patients, for whom cloxacillin (patient 25) or amoxicillin (patient 16) had been suspected, had negative tests for the suspected drug but positive results for other BL and were thus considered BL-allergic and included in the above 22 positive patients. Among the 22 patients explored by P-IDR, 2 had positive P-IDR test results for a drug negative by PT (patients 7 and 10 in table 2); these 2 patients are included in the 22 positive patients.

Cross-reactivity was diagnosed in 14/22 patients (63.6%, 95% CI [43.6–83.7]) with positive BL results. Among the 19 patients with penicillin-suspected CADR, 11 showed reaction to another penicillin (58%): in the 18 patients with amoxicillin-suspected non-immediate CADR, 10 (55.6%) showed reaction to at least one other BL subclass: 9 (50%) to other penicillin subclasses (G, V, M; ureidopenicillins) and 3 to non-aminocephalosporins (16.6%). The patient with cloxacillin-suspected non-immediate CADR reacted to G- and V-penicillin.

Among the 4 positive patients with non-aminocephalosporin-suspected non-immediate CADR, 2 showed reaction to a penicillin and 2 to another cephalosporin subclass. Within the whole cohort, no patient with penicillin- or cephalosporin-suspected non-immediate CADR showed cross-reactivity with cephalexin (aminocephalosporin) or other first-class cephalosporin or with aztreonam (tested in 30 patients) or carbapenems (tested in 22 patients).

PTs were sufficient to show cross-reactivity in 13/14 (92.9%) patients; for only one patient (patient 10 in table 2) with amoxicillin-induced MPE (time to onset = 4 days) was cross-reactivity diagnosed by a positive P-IDR with a negative PT.

Table 2

According to the type of CADR, skin tests were positive for 9/27 (33.3%) patients with MPE, 10/23 (43.5%) with AGEP, 3/3 (100%) with DRESS and none of the 3 patients with bullous drug reactions.

In total, cross-reactivity was observed in 5/9 (50%) patients with MPE, 7/10 (70%) with AGEF, and 1/3 (33.3%) with DRESS.

Discussion

Our study is the largest one to investigate cross-reactivity among BL antibiotics in non-immediate CADR including severe CADR (table 3).¹⁴⁻²¹ It is also the first one with a clearly late notified delay of onset for patients with MPE¹³.

Table 3

We showed a high frequency of cross-reactions between BL subclasses (63.6% among test-positive patients) in non-immediate CADR, which emphasizes the importance of skin testing of all BL subclasses to further assess allowed drugs. Moreover, the large allergologic exploration identified 2 patients who would have not been diagnosed if tests had been limited to the suspected drug.

Our results demonstrate an important rate of cross-reactions (55%, CI [33.2 – 76.8]) among penicillin-suspected non-immediate CADR. These results encourage avoiding the whole penicillin class in case of positive tests or strong suspicion of allergy to one drug in this class. Challenges should be discussed for negative tested drugs only when no substitution inside BLs is possible.

For allergy to penicillin, we found cross-reactivity with cephalosporins in 3/18 (16.5%) BL-positive patients, in accordance with previous publications¹⁴⁻¹⁶.

Regarding allergies between penicillins and cephalosporins, cross-reactions are classically described between amoxicillin and aminocephalosporins of the first class that share a aminobenzyle R1-side-chain (cefactor, cefadroxil, cephalexin) similar to amoxicillin¹⁵. All our patients were tested with cephalexin and all amoxicillin-positive patients had negative test results for that drug. Among the cephalosporin-suspected cases, cross-reactivity concerned the second- and third-class cephalosporins and no case involved an aminocephalosporin.

As previously published (Table 3)¹⁷⁻²¹, we did not find any cross-reactivity between penicillins or cephalosporins and aztreonam or carbapenems. These two later subclasses of BL drugs thus seem

safe alternatives for patients with penicillin- or cephalosporin-induced late CADR and even before allergologic investigation³¹ in case of emergency.

Our results confirm a PT sensitivity of about 30%, which is similar to previous reported series with this method in non-immediate CADR^{21-23, 25}. Among the 22 patients who underwent P-IDRs after a negative PT result, only 2 had a positive P-IDR associated with a negative PT result. So, in our opinion, PTs, that are the only tests recommended for DRESS and bullous CADR^{21-23, 25}, seem also sufficient for AGEP and for MPE with late delay of onset. Moreover, PT are cheaper, faster and easier to perform in routine practice in comparison to intradermic tests. However, as recently published, a collaboration of large international networks is needed to develop and standardize *in vivo* diagnostic approaches^{12,24}.

A limitation of our study is its retrospective design, but clinical data at the acute phase were correctly collected because all patients received care on our department. Allergologic explorations were always performed with the same protocol by 2 practitioners who collected data in a standardized form. Despite the fact that our study had a small number of patients with BL-suspected non-immediate CADR, we report the largest series of allergologic exploration in severe CADR^{21-23, 25} and MPE with longer than 2 days delay of onset. Another limitation is that cross-reactivity was based only on tests, as done in previous published studies. Rechallenge of the positive cross-reacting drugs is not performed in routine practice and does not either seem suitable in prospective studies. Rechallenge of the negative-tests drugs to exclude cross reactivity does not seem either suitable regarding to the low sensitivity of the tests and because substitutions are often possible.

As a conclusion, our study claims for a large BL allergologic exploration after a non-immediate CADR to prove allergy and to investigate cross-reactions. PT only may be sufficient for severe cases, including AGEP, and for long delayed MPE. Frequent cross-reactivity among penicillins encourage stopping the whole family when allergy is proven or greatly suspected for even one of its subclasses and to test cephalosporins, aztreonam and carbapenems to find an alternative drug.

References

- 1 Fiszenson-Albala F, Auzerie V, Mahe E, et al., A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol*. 2003;1018-22.
- 2 Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O, Severe cutaneous adverse reactions to drugs. *Lancet*. 2017;28; 1996–2011.
- 3 Jannic A, Servy A, Chevalier X, et al., Self-diagnosed drug allergies: the belief of patients. *J Eur Acad Dermatol Venereol*. 2017: e524-e526.
- 4 Amsler E, Soria A. Allergies aux bêta-lactamines. *La Revue de Médecine Interne*. 2017;1:737–48
- 5 Shenoy ES, Macy E, Rowe T, et al., Evaluation and Management of Penicillin Allergy: A Review. *JAMA*. 2019;15:188–99.
- 6 Blumenthal KG, Peter JG, Trubiano JA et al., Antibiotic allergy. *Lancet*. 2019;12:183–98.
- 7 McDanel J, Perencevich E, Diekema D, et al. Comparative effectiveness of betalactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. *Clin Infect Dis* 2015; 61:361–367
- 8 Macy E, Contreras R. Healthcare use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014; 133:790–6.
- 9 Jeffres MN, Narayanan PP, Shuster JE, et al., Consequences of avoiding β -lactams in patients with β -lactam allergies. *J Allergy Clin Immunol*: 2016;137:1148-53.
- 10 MacFadden DR, LaDelfa A, Leen J, et al., Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. *Clin Infect Dis*. 2016;1:904–10.
- 11 Romano A, Blanca M, Torres MJ, et al., Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy*. 2004;59:1153–60.
- 12 Torres MJ, Celik GE, Whitaker P, et al. A EAACI drug allergy interest group survey on how European allergy specialists deal with β -lactam allergy. *Allergy*. 2019;00:1–11
- 13 Brockow K, Arderon-Jones M, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019 74:14-27
- 14 Romano A, Gaeta F, Valluzzi RL, et al. Diagnosing nonimmediate reactions to cephalosporins. *J Allergy Clin Immunol*. 2012;129:1166–9
- 15 Trcka J, Seitz CS, Bröcker E-B, et al. Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. *Journal of Antimicrobial Chemotherapy*. 2007;1:60:107–11.
- 16 Buonomo A, Nucera E, Pecora V, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. *J Invest Allergol Clin Immunol*. 2014;24:331–7.
- 17 Schiavino D, Nucera E, Lombardo C, et al. Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to beta-lactams. *Allergy*. 2009;64:1644–8.

- 18 Romano A, Gaeta F, Valluzzi RL, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. *Allergy*. 2013;68:1618–21.
- 19 Buonomo A, Nucera E, Pasquale TD, et al. Tolerability of Aztreonam in Patients with Cell-Mediated Allergy to β -Lactams. *IAA*. 2011;155:155–9
- 20 Romano A, Gaeta F, Valluzzi RL, et al., Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol*. 2016;138:179–86.
- 21 Pinho A, Coutinho I, Gameiro A, et al., Patch testing - a valuable tool for investigating non-immediate cutaneous adverse drug reactions to antibiotics. *J Eur Acad Dermatol Venereol*. 2017;31:280–7.
- 22 Wolkenstein P, Chosidow O, Fléchet ML, et al. Patch testing in severe cutaneous adverse drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. *Contact Derm*. 1996;35:234–6
- 23 Assier H, Valeyrie-Allanore L, Gener G, et al., Patch testing in non-immediate cutaneous adverse drug reactions: value of extemporaneous patch tests. *Contact Derm*. 2017;77:297–302
- 24 Phillips EJ, Bigliardi P, Bircher AJ, et al. Controversies in drug allergy: Testing for delayed reactions. *J Allergy Clin Immunol*. 2019;143:66–73.
- 25 Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol*. 2013;168:555–62
- 26 Romano A, Viola M, Mondino C, et al. Diagnosing nonimmediate reactions to penicillins by in vivo tests. *Int Arch Allergy Immunol*. 2002;129:169–74.
- 27 Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Derm*. 2001;45:321-328.
- 28 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Derm*. 2015;73:195-221.
- 29 Brockow K, Garvey LH, Aberer W, et al. ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68:702-12.
- 30 Bursztejn AC, Rat AC, Tréchet P et al. Résultats des tests cutanés dans l'exploration des toxidermies, *Annales de dermatologie et de vénérologie*, 2010;137:688-694
- 31 Sodhi M, Axtell SS, Callahan et al. Is it safe to use carbapenems in patients with a history of allergy to penicillin? *Journal of Antimicrobial Chemotherapy*. 2004;54:1155-1157.

Table 1: Characteristics of patients in the study (n=56)		
Male sex (N,%)		28 (50)
Age (years), median [IQR]		59 [40–66]
Suspected beta-lactam (N,%)	Amoxicillin	46 (82.1)*
	M-penicillin	3 (5.4)
	Cephalosporins	
	C1G	1 (1.8)
	C2G	3 (5.4)
	C3G	3 (5.4)*
	Aztreonam	1 (1.8)
Time between the non-immediate CADR and allergologic exploration (days), median [IQR] (n=45)		124 [83–180]
Pattern of non-immediate CADR (N,%)	MPE	27 (48.2)
	AGEP	23 (41.1)
	DRESS	3 (5.4)
	Bullous reactions (FDE/SJS)	3 (5.4)
*One patient with both amoxicillin and cefpodoxime as suspects		
IQR: interquartile range, CADR: cutaneous adverse drug reaction, MPE: maculopapular exanthema, AGEP: acute generalized exanthematous pustulosis, DRESS: drug reaction with eosinophilia and systemic symptoms, FDE: fixed drug eruption, SJS: Stevens-Johnson syndrome, C1G: first-class cephalosporin; C2G: second-class cephalosporin; C3G: third-class cephalosporin		

Table 2: results of skin tests in the 22 patients with positive results

Patient number	Age	Sex	Suspected drug	Cross-reactions	Positive skin test									
					Penicillins				AC	NAC			Others beta-lactams	
					amoxicillin	M-penicillin	G/V-penicillin	piperacillin	C1G	C1G	C2G	C3G	aztreonam	carbapenem
DRESS														
1	59	F	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0
2	33	F	amoxicillin	M-penicillin, G/V-penicillin	PT	PT	PT	0	0	0	0	0	0	0
3	58	M	cefoxitine	0	0	0	0	0	0	0	PT (cefoxitine)	0	0	0
MPE														
4	66	F	amoxicillin	M-penicillin	PT	PT	0	0	0	0	0	0	0	0
5	42	M	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0
6	49	M	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0
7	29	M	amoxicillin	0	P-IDR	0	0	0	0	0	0	0	0	0
8	62	M	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0

9	72	F	amoxicillin	G/V- penicillin	PT	0	PT	0	0	0	0	0	0	0
10	63	M	amoxicillin	piperacillin	P-IDR (doubtful PT)	0	0	P-IDR	0	0	0	0	0	0
11	74	M	amoxicillin	C3G	PT	0	0	0	0	0	0	PT (cefotaxime)	0	0
12	78	M	amoxicillin	M- penicillin, G/V- penicillin, C3G	0	PT	PT	0	0	0	0	PT (cefotaxime, ceftriaxone)	0	0
AGEP														
13	59	M	amoxicillin	M- penicillin, G/V- penicillin	PT	PT	PT	0	0	0	0	0	0	0
14	24	M	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0
15	40	M	amoxicillin/ cefepodoxime	M- penicillin, G/V-	PT	PT	PT	0	0	0	0	PT (cefotaxime)	0	0

				penicillin										
16	60	M	amoxicillin	M- penicillin, G/V- penicillin	PT	PT	PT	0	0	0	0	0	0	0
17	33	F	amoxicillin	G/V- penicillin	PT	0	PT	0	0	0	0	0	0	0
18	33	F	amoxicillin	M- penicillin, G/V- penicillin	PT	PT	PT	0	0	0	0	0	0	0
19	66	M	amoxicillin	0	PT	0	0	0	0	0	0	0	0	0
20	48	M	cloxacillin	G/V- penicillin	0	0	PT	0	0	0	0	0	0	0
21	49	F	cefuroxime	amoxicillin, M- penicillin, C3G	PT	PT	0	0	0	0	0	PT (cefotaxime)	0	0
22	86	F	ceftriaxone	C2G	0	0	0	0	0	0	PT (cefuroxime,	PT (ceftriaxone,	0	0

											cefoxitine)	cefotaxime, ceftazidime)		
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AC: aminocephalosporin, AGEF: acute generalized exanthematous pustulosis, C1G: first-generation cephalosporin, C2G: second-generation cephalosporin, C3G: third-generation cephalosporin, DRESS: drug reaction with eosinophilia and systemic symptoms, MPE: maculopapular exanthema, NAC: non-aminocephalosporin, P-IDR: pricks or intradermal test, PT: patch-test

Table 3: Previously published studies of epicutaneous tests for cross-reactivity diagnosis in non-immediate CADR				
Author (Year)	Population	Details of CADR given in the text	Tests	Results
Romano (2002) (26)	259 penicillin-induced CADR	Maculopapular rash: 173 Urticaria: 33 Erythema: 22 Angioedema: 13 Urticaria/angioedema: 13 Local reaction: 1 Other manifestations: 4	G/A penicillin	Positive tests for A penicillin: 94/259 (36.1%) Cross-reactivity: in 94 amoxicillin-reacting patients: 29 (30.9%) to G-penicillin
Trcka (2007) (15)	71 amoxicillin-induced exanthemas	Maculopapular exanthema: 57 Urticaria: 9 Erythema multiforme: 2 Undefined: 3	C3G and G/A penicillin	Positive skin test (details not shown) to G-penicillin: 20/71 (40.8%) No positive test to cefpodoxime and cefixime
Romano (2012) (14)	105 CADR to cephalosporins	Maculopapular rash: 52 Urticaria: 37 Erythema: 26 Edema: 13 Urticaria/angioedema: 13 Other: 3	G/A penicillins and C1G, C2G, C3G	PT to culprit CS: 3/105 P-IDR to culprit: 7/105 (including 3 PT-positive patients) Cross-reactivity to A penicillin: all patients (3) with positive PT, none with positive PT/negative P-IDR
Buonomo (2014) (16)	97 penicillin-induced CADR hour with positive prior PT	Delayed urticaria: 32 Maculopapular exanthema: 26 Maculopapular exanthema + angioedema: 25 Delayed appearing urticaria + angioedema: 17 Generalized erythema: 16 Angioedema: 9 Generalized itching: 1 Contact dermatitis: 1 SJS: 1 Erythema multiforme: 1	C1G, C2G, C3G	PT positive to CS: 17/97 (17.5%) (10 cephalexin, 9 cefaclor, 5 cefuroxime) No positive P-IDR
Pinho (2017) (21)	122 CADR to penicillin (101 to amoxicillin) 91 CADR to cephalosporins 5 CADR to	Amoxicillin: MPE: 78, DRESS: 9 C3G: DRESS: 2 M-penicillin: MPE: 8, AGEP: 1 G-penicillin: MPE: 12†	A series of systemic antibiotics	PT: 31/122 (25.4%) to penicillin, 4/91 (4.4%) to CS, 1/5 (20%) to carbapenems Cross-reactivity: in 25 amoxicillin-reacting patients 9 (36%) to other penicillin, 1 to CS (4%)

	carbapenems			
Buonomo (2011) (19)	78 patients with CADR to various BL	Urticaria: 34 Urticaria + angioedema: 15 Maculopapular exanthema: 13 Erythema: 13 Maculopapular exanthema + angioedema: 12 Angioedema: 9 Erythema + angioedema: 3 Contact dermatitis: 1 SJS: 1	Penicillins, CS, AZM	No positive test to AZM
Romano (2016) (20)	214 CADR to penicillin with positive prior PT	Maculopapular exanthema: 146 Maculopapular exanthema plus edema: 114 Erythema: 14 Erythema plus edema: 7 Edema: 6 TEN: 5 AGEP: 3 Local reaction: 3 Urticaria: 2 Others: 4	C1G, C2G, C3G, AZM	No positive test for C2, C3, AZM 15/213 (7%) positive PT to C1G, 40 (18.8%) positive P-IDR to C1G
Romano (2013) (18)	204 CADR to penicillins	Maculopapular exanthema plus edema: 116 Erythema: 12 Bullous exanthema: 3 Erythema plus edema: 7 Local reaction: 3 Urticaria: 2 Toxic epidermal necrolysis: 4 AGEP: 3 Others: 4	Penicillins and CP	No positive test to CP

Schiavino (2009) (17)	73 CADR to BL with positive prior PT	Urticaria: 30 Maculopapular rash: 13 Erythema: 13 Urticaria + angioedema: 13 Maculopapular rash + angioedema: 12 Angioedema: 8 Erythema + angioedema: 3 Contact dermatitis: 1 SJS: 1	PT/P-IDR with penicillin, CS and CP	PT to imipenem: 4/73 (5.5%) No positive P-IDR
AZM: aztreonam, CP: carbapenems, CS: cephalosporin, C1G: first-class cephalosporin, C2G: second-class cephalosporin, C3G: third-class cephalosporin †No further details given in the text; in bold, well defined late CADR (according to European Academy of Allergy and Clinical Immunology) (12)				