

Long-term reproducibility of positive patch test reactions in patients with non-immediate cutaneous adverse drug reactions to antibiotics

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Summary

Background. As in contact allergy, T cell-mediated hypersensitivity in non-immediate (NI) cutaneous adverse drug reactions (CADRs) to antibiotics is considered to be lifelong, but, in this setting, patch tests have rarely been repeated after long time intervals.

Objective. To evaluate the long-term reproducibility of positive patch test reactions to antibiotics in patients with NI CADRs.

Methods. Fifty-six patients with NI CADRs to antibiotics who had relevant positive reactions during patch testing were invited to repeat patch tests with a similar antibiotic series 2–15 years thereafter.

Results. Twenty patients were included (9 males and 11 females; mean age 54.6 years): 18 with maculopapular exanthema, 1 with drug hypersensitivity syndrome, and 1 with acute generalized exanthematous pustulosis. Results were reproducible in 17 of 20 patients after a mean interval of 6.0 years (range 2–14.7 years). Concerning β -lactams, 7 of 8 patients remained positive for aminopenicillins, 4 of 4 for isoxazolyl penicillins, and 1 for cefoxitin. Patch test results were also reproducible for clindamycin in 5 of 7 patients, for vancomycin in 1 patient, and for spiramycin in 1 patient. Reproducibility was not affected by the time interval between tests, sex, or age at testing.

Conclusions. In the context of NI CADRs, we showed high reproducibility of positive patch test reactions to various antibiotics, even after several years.

Key words: antibiotics; cutaneous adverse drug reactions; delayed hypersensitivity; patch test; reproducibility.

Antibiotics, which are some of the most frequent causes of non-immediate (NI) cutaneous adverse drug reactions (CADRs), often elicit positive patch test reactions (1–4).

Current guidelines recommend that, in the context of NI CADRs to antibiotics, patch tests should be performed from 3–6 weeks up to 3–6 months after the complete

resolution of skin eruptions (5, 6). However, positive patch test reactions can be observed from years to decades after the initial skin eruption (7). Moreover, for many years after resolution of the NI CADRs, peripheral blood mononuclear cells may remain susceptible to activation by the specific culprit drug, suggesting a long-lasting memory even without further exposure (8).

As in contact allergy to small chemicals, T cell-mediated hypersensitivity in patients with NI CADRs to antibiotics is considered to be lifelong (9, 10). In patients with contact dermatitis, the long-term reproducibility of positive patch test reactions may vary from 66% to 71%, and does not seem to be affected by the time elapsed between tests (9, 11). In patients with occupational contact dermatitis caused by penicillins, it was

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Table 1. Allergens included in our patch testing series of antibiotics

Allergens supplied by Chemotechnique Diagnostics	Allergen concentration	Allergens prepared in-house	Allergen concentration
Amoxicillin trihydrate	10% pet.	Amoxicillin–clavulanic acid ^a	10% pet.
Benzylpenicillin potassium salt	10% pet.	Ampicillin ^b	10% pet.
Cefalexin	10% pet.	Cefazolin ^b	10% pet.
Cefradine	10% pet.	Cefoxitin ^b	10% pet.
Cefotaxime sodium salt	10% pet.	Ceftizoxime ^a	10% pet.
Cefuroxime sodium	10% pet.	Ceftriaxone ^c	10% pet.
Ciprofloxacin hydrochloride	10% pet.	Cefuroxime ^c	10% pet.
Clarithromycin	10% pet.	Co-trimoxazole ^a	10% pet., aq.
Clindamycin phosphate	10% pet.	Imipenem–cilastatin ^c	10% pet.
Co-trimoxazole	10% pet.	Levofloxacin ^a	10% pet.
Dicloxacillin sodium salt hydrate	10% pet.	Lomefloxacin ^a	10% pet.
Doxycycline monohydrate	10% pet.	Meropenem ^c	10% pet.
Erythromycin base	10% pet.	Metronidazole ^b	10% pet.
Minocycline hydrochloride	10% pet.	Piperacillin–tazobactam ^c	10% pet.
Norfloxacin	10% pet.	Teicoplanin ^c	10% pet.
Spiramycin base	10% pet.	Vancomycin ^c	10% pet.

pet. and aq. as detailed by the authors (4).

^aAllergen prepared from tablet or capsules obtained from the hospital pharmacy.

^bAllergen prepared from the pure drug supplied by a pharmaceutical company.

^cAllergen prepared from powder from the hospital pharmacy for intravenous injection.

shown that patch test reactivity did not disappear over time, although the intensity could fluctuate (12).

Nevertheless, in the setting of NI CADR to antibiotics, patch tests have rarely been repeated for assessment of the long-term reproducibility of initially positive results. The present study thus addressed the long-term reproducibility of positive patch test reactions to antibiotics in patients with NI CADR.

Patients and Methods

We reviewed patch test data and clinical files of 260 patients referred to our dermatology clinic between the years 2000 and 2014 for the study of a well-characterized NI CADR to antibiotics. Fifty-six patients (21.5%) had positive patch test reactions to antibiotics, and were then invited, by telephone, to perform new patch tests during the period May 2015 to May 2016, at least 2 years after the first patch tests.

For those who accepted the invitation, patch tests were conducted, after informed consent had been obtained, according to ESCD and European Network on Drug Allergy/European Academy of Allergy and Clinical Immunology guidelines for skin testing in patients with CADR (5, 6, 13). Patch tests were applied to the upper back for 2 days, with Finn Chambers[®] on Scanpor[®] tape (Epitest, Tuusula, Finland) or IQ-Ultra Chambers[™] (Chemotechnique Diagnostics, Vellinge, Sweden). Readings were performed on day (D) 2 and D3 or D4, with a late reading on D7 whenever initial results were negative (5).

All patients were tested with a series of systemic antibiotics, including those supplied by Chemotechnique Diagnostics, and with powder of the commercial drugs obtained from capsules/tablets or from intravenous preparations, appropriately diluted in pet. or aq. to obtain concentrations of 10% of the active ingredient (Table 1). As controls for the allergens prepared at our laboratory, we tested all other patients who were exposed or reacted to other culprit antibiotics. According to patients' clinical history, we also repeated patch testing with other culprits, namely with anticonvulsant and antiviral drugs.

Only 1+ (erythema and infiltration of the whole patch test area) or more intense reactions were considered to be positive. Reproducibility of positive patch test results was defined as the persistence of a positive reaction over time, regardless of its intensity. We assessed: (i) the long-term reproducibility of patch test results in patients with culprit and cross-reacting antibiotics; and (ii) variation in intensity of positive patch test reactions over time.

Patients were also asked about accidental re-exposure to culprit antibiotic(s) or new episodes of CADR since the first patch tests.

Data were statistically analysed with SPSS software (Version 21.0; IBM, Armonk, NY, USA). We used Fisher's exact test to examine the influence of sex on the reproducibility of patch test results. The *t*-test for independent samples was used to evaluate whether the reproducibility of patch test results was influenced by age at first or second patch test, or by the time interval between patch tests. *p*-Values < 0.05 were considered to be significant.

Results

Characterization of the studied population

Of the 56 invited patients, 20 (9 males; 11 females) agreed to repeat patch tests (35.7% response rate), 18 with history of maculopapular exanthema (MPE), 1 with drug rash with eosinophilia and systemic symptoms (DRESS), and 1 with acute generalized exanthematous pustulosis (AGEP) (Table 2). The mean age at first patch test was 48.2 ± 16.6 years (median 52.0 years, range 17–72 years).

In patients with MPE, culprit antibiotics with previous positive patch test reactions included amoxicillin (6 cases), flucloxacillin (3), clindamycin (7), cefoxitin (1), spiramycin (1), and vancomycin (1). In one patient (case 10), MPE was attributed both to spiramycin and clindamycin. In the single case of DRESS (case 12), the culprits were carbamazepine, acyclovir, and amoxicillin (all prescribed in the setting of herpes simplex virus 1 meningitis), and the only case of AGEP (case 9) was attributed to amoxicillin and flucloxacillin.

This population had 37 initially positive patch test reactions to antibiotics, of which 15 were probably cross-reactions between β -lactams.

Five patients had a history of accidental re-exposure to culprit antibiotics prior to the first positive patch test reactions. However, after those first tests, none was subsequently exposed to the positive culprits.

Reproducibility of positive patch test results

Among the 20 patients included, the mean interval between tests was 6.0 ± 3.9 years, (median 5.4 years, range 2.0–14.7 years), and the mean age at new patch testing was 54.6 ± 17.8 years (median 57.5 years, range 20–79 years). Long-term reproducibility of positive patch test results with culprit antibiotics was observed in 17 of 20 (85%) patients (8 males; 9 females) (Table 2).

Regarding the type of CADR, patch test results with antibiotics were reproducible in 16 of 18 (88.9%) cases of MPE, in 1 case of AGEP, but not in the single case of DRESS.

Concerning the type of culprit antibiotic drug, 7 of 8 patients remained positive for aminopenicillins (amoxicillin and cross-reacting ampicillin), 4 of 4 for isoxazolylic penicillins (flucloxacillin and cross-reacting dicloxacillin) and 1 of 1 for cefoxitin after mean intervals of 6.5, 7.4 and 2.2 years, respectively. We observed long-term patch test reactivity in all 10 cases of MPE induced by β -lactams after a mean interval of 6.2 years. In the patient with AGEP (case 9), patch tests remained positive for amoxicillin and flucloxacillin, both culprits, but were also positive for other β -lactams, such as ampicillin,

dicloxacillin, benzylpenicillin, and piperacillin, after 6.5 years. The single patient who lost reactivity for aminopenicillins (case 12) had a history of DRESS, but patch test results for the other culprits, acyclovir and carbamazepine, were still positive after 3.7 years.

For clindamycin, positive patch test results were reproducible in 5 of 7 patients, all with MPE, after a mean of 6.6 years.

One patient (case 3) with a previous history of MPE after treatment with clindamycin, when accidentally re-exposed to clindamycin in combination with cefazolin for the treatment of erysipelas, developed a new MPE. The patch tests conducted at that time showed reactivity only to clindamycin. Two years later, the patient was again exposed to cefazolin (without clindamycin), and had another episode of MPE, but no patch tests were performed. Nevertheless, when we repeated the patch tests (11.5 years after the initial tests), clindamycin remained reactive, but *de novo* reactivity was observed with cefazolin; a positive reaction was also observed with cefoxitin, but was probably a cross-reaction, as the patient had never been previously exposed to it.

Single reproducible patch test results were also seen with vancomycin (1 patient) and spiramycin (1 patient), after 2.5 and 5.5 years, respectively, and after MPE.

The majority of new patch test reactions were positive on D2, whereas none occurred after D4 (Table 2). They were mostly 1+ (13/35) or 2+ (14/35) reactions, and only 6 of 35 were strong (3+) reactions. No flare-up of CADRs occurred during patch testing. All positive reactions were considered to be relevant or attributable to cross-reactions. No unexplained positive reactions were observed within the entire series of antibiotics tested.

Variation in the intensity of patch test results

Of the 37 positive patch test reactions to antibiotics observed initially, including 15 cross-reactions, 4 did not recur in retests (10.8%), whereas the other 33 (89.2%) remained positive: in 20 of 33 (60.6%) the same intensity of reaction was observed, in 9 of 33 (27.3%) the intensity decreased, and in 4 of 33 (12.1%) intensity increased (Table 3).

Concerning the intensity of the 37 initial reactions, 1+ reactions were reproducible (with the same intensity) in 6 of 10 (60%) instances, 2+ reactions in 10 of 18 (55.6%), and 3+ reactions in 4 of 9 (44.4%). Therefore, most reactions (20/37; 54.1%) showed the same intensity over time.

There were no significant differences between the sexes ($p = 0.67$), between age at first patch test ($p = 0.21$), between age at second patch test ($p = 0.15$) or between

Table 2. Characterization of patients with initially positive patch test (PT) reactions who underwent new PTs

Case no./sex	Age at first PT (years)	Age at new PT (years)	Interval between PTs (years)	CADR	Culprit	First PT reactions: readings at D2 and D3/D4		New PT reactions: readings at D2 and D3/D4	
1/F	31	46	14.7	MPE	AMX ^a	AMX	++	AMX	++
						AMP	++	AMP	+
2/M	37	49	12.5	MPE	AMX	AMX	++	AMX	++
						AMP	++	AMP	+++
3/F	64	76	11.5	MPE	Clindamycin ^a Cefazolin ^b	Clindamycin	++	Clindamycin	+
						Cefazolin	Neg.	Cefazolin	+
						Cefoxitin ^c	Neg.	Cefoxitin ^c	+
4/F	51	60	10.7	MPE	Flucloxacillin	Flucloxacillin	+++	Flucloxacillin	++
						Dicloxacillin	+++	Dicloxacillin	++
						Benzylpenicillin	+++	Benzylpenicillin	+
5/F	33	42	8.52	MPE	Clindamycin	Clindamycin	++	Clindamycin	Neg.-NR
6/F	67	75	7.9	MPE	Clindamycin ^a	Clindamycin	++	Clindamycin	+
7/F	72	79	7.4	MPE	AMX	AMX	+++	AMX	+
						AMP	+++	AMP	+
8/F	55	62	7.0	MPE	Clindamycin	Clindamycin	+	Clindamycin	+
9/M	36	43	6.5	AGEP	AMX Flucloxacillin	AMX	+	AMX	++
						AMP	+	AMP	+
						Flucloxacillin	+++	Flucloxacillin	+++
						Dicloxacillin	++	Dicloxacillin	++
						Benzylpenicillin	++	Benzylpenicillin	++
						Piperacillin	++	Piperacillin	++
10/M	56	62	5.8	MPE	Spiramycin Clindamycin	Clindamycin	+	Clindamycin	++
						Spiramycin	+++	Spiramycin	+++
11/M	70	85	4.9	MPE	Flucloxacillin	Dicloxacillin	+	Dicloxacillin	+
						Flucloxacillin	+	Flucloxacillin	+
12/M	51	54	3.7	DRESS	AMX Carbamazepine Acyclovir	AMX	+	AMX	Neg.-NR
						AMP	++	AMP	Neg.-NR
						Carbamazepine	+	Carbamazepine	+
						Acyclovir	+	Acyclovir	+
13/F	35	39	3.4	MPE	Clindamycin	Clindamycin	+	Clindamycin	Neg.-NR
14/F	53	55	2.6	MPE	AMX	AMX	++	AMX	+
						AMP	++	AMP	+
15/M	26	28	2.6	MPE	AMX	AMX	++	AMX	++
						AMP	++	AMP	+++
16/M	17	20	2.5	MPE	Vancomycin ^a	Vancomycin	+	Vancomycin	+
17/F	60	62	2.3	MPE	AMX	AMX	++	AMX	++
						AMP	++	AMP	++
18/M	64	65	2.2	MPE	Cefoxitin	Cefoxitin	+	Cefoxitin	+
19/M	60	62	2.0	MPE	Clindamycin ^a	Clindamycin	++	Clindamycin	++
20/F	26	28	2.0	MEP	Flucloxacillin	Flucloxacillin	+++	Flucloxacillin	+++
						Dicloxacillin	+++	Dicloxacillin	+++

AGEP, acute generalized exanthematous eruption; AMP, ampicillin; AMX, amoxicillin; CADR, cutaneous adverse drug reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; F, female; M, male; MPE, maculopapular exanthema; Neg., negative reaction; Neg.-NR, negative, non-reproducible reaction; PT, patch tests.

^aAccidental positive re-exposure before first patch tests, confirming the imputability of the culprits.

^bAccidental re-exposure following the first patch tests.

^cPossible cross-reaction with cefazolin.

test intervals ($p=0.47$) when the non-reproducible reactions were compared with those that were reproducible. Moreover, concerning these same variables, no significant differences were observed when the reaction intensities that remained or increased were compared with those whose intensity decreased or that vanished.

Discussion

Previous studies showed that, in patients with immediate CADRs to antibiotics, hypersensitivity tends to vanish, with reductions in specific IgE and prick test reactions, in the absence of subsequent exposure to the culprit

Table 3. Reproducibility and variation in the intensity of patch test (PT) results

Patch tested antibiotic	Positive cases First PT	Positive cases New PT	Positive reproducibility (%)	Increased positive reaction	Equally positive reaction	Decreased positive reaction
Aminopenicillins – AMX	8	7	87.5	1	4	2
Aminopenicillins – AMP ^a	8	7	87.5	2	2	3
Isoxazolyl penicillins – flucloxacillin	4	4	100	0	3	1
Isoxazolyl penicillins – dicloxacillin ^a	4	4	100	0	3	1
Penicillins – benzylpenicillin ^a	2	2	100	0	1	1
Cephalosporins – cefoxitin	1	1	100	0	1	0
Ureidopenicillins – piperacillin ^a	1	1	100	0	1	0
Lincosamides – clindamycin	7	5	71.4	1	3	1
Macrolides – spiramycin	1	1	100	0	1	0
Glycopeptides – vancomycin	1	1	100	0	1	0
Overall	37	33	82.9	4/33 (12.1%)	20/33 (60.6%)	9/33 (27.3%)

AMP, ampicillin; AMX, amoxicillin.

^aNon-culprit cross-reacting antibiotic.

antibiotic (14, 15). It is estimated that 50% of patients with IgE-mediated penicillin allergy apparently lose their sensitivity 5 years after the skin eruption, increasing to ~80% at 10 years (16, 17).

In the setting of NI CADR to antibiotics, few studies have utilized patch testing to evaluate the long-term behaviour of this type of hypersensitivity, and in most cases the tested antibiotics were penicillins (18, 19). To the best of our knowledge, there are no previously published reports on the reproducibility of positive patch test results with antibiotics other than penicillins.

In 1993, Romano et al. showed that, in 23 patients with a previous CADR, namely urticaria, angioedema, or MPE, to amoxicillin and ampicillin, retesting with the culprit antibiotic at least 1 year after the first patch tests gave persistently positive results in all cases. Sixteen (69.5%) patients also showed results similar to those of their initial patch tests. However, the study did not discriminate the proportion of cases presenting with MPE (18). In our series, more than half of initially positive reactions persisted at the same intensity, and patient age, patient sex and the time interval between tests did not affect the variation in intensity of the patch test results.

Bruynzeel and van Ketel retested 15 patients who had previous positive patch test reactions to amoxicillin, ampicillin, or phenethicillin (19). They repeated patch tests sequentially, between 10 and 100 weeks after the initial drug eruption, with the culprits and also with benzylpenicillin, cloxacillin, cefadrin, and cephalothin. In 8 patients, they observed an increasing number of positive reactions, and 7 of these 8 patients also showed increasingly severe reactions over time. Conversely, in 5 patients, the number and intensity of reactions decreased. Two other patients showed

no reactions upon retesting. The type of previous NI CADR was not stated, and the authors did not distinguish between reactivity to culprits and reactivity to other tested antibiotics.

In our study, among the 10 MPE cases and 1 AGEF case attributable to β -lactams, there was 100% reproducibility of patch test results, as suggested by previously mentioned studies. Long-term reproducibility was also the rule for the cross-reacting antibiotics.

In the single case of DRESS, reproducibility was lost for amoxicillin but remained unchanged for carbamazepine and acyclovir. Previous reports had already suggested that exposure to amoxicillin during DRESS caused by carbamazepine might induce long-term hypersensitivity to both drugs (20). We consider that the synchronous occurrence of a herpes virus infection and systemic exposure to carbamazepine, acyclovir and amoxicillin might enhance the sensitization (with more efficient presentation of chemical antigens such as amoxicillin to antigen-presenting cells) and/or effector phases of CADR, which ultimately translate into positive patch test reactions to all possible culprits (20, 21). However, with a time interval of 3.7 years between tests, in the absence of viral infection and systemic exposure to carbamazepine and/or acyclovir, the reactivity to amoxicillin was eventually lost in new patch tests.

The sensitivity of patch testing for diagnosing NI CADR to clindamycin was previously reported to be 19–30% in patients with NI CADR (2, 22). In the present study, we have shown that >70% of cases still react to this culprit without additional exposure.

The two additionally tested and non-related drugs, vancomycin and spiramycin, also elicited positive reactions in patch testing. These antibiotics are not typically

among the culprits most frequently detected by patch testing in the context of NI CADR; however, long-term reproducibility might be expected (4).

In conclusion, in most cases of NI CADR induced by antibiotics – especially by β -lactams and clindamycin, but possibly also by vancomycin or spiramycin – T cell hypersensitivity assessed by patch tests lasted for several years. These findings support the recommendation for lifelong avoidance of culprit antibiotics following an NI

CADR, but also emphasize the role of patch tests as a diagnostic tool in patients with NI CADRs, even when the adverse reaction occurred several years earlier, thus allowing retrospective diagnosis.

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