

Patch testing for the investigation of nonimmediate cutaneous adverse drug reactions: A prospective single center study



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Clinical Implications

- Patch testing is a safe, effective, and useful diagnostic tool for the investigation of cutaneous adverse drug reactions and demonstrates excellent concordance with intradermal testing. Quality improvement is a valuable resource for incorporating patch testing into standard drug allergy practice.

TO THE EDITOR:

Nonimmediate cutaneous adverse drug reactions (CADRs) are typically divided into 5 major clinical phenotypes: maculopapular exanthema (MPE), fixed drug eruption (FDE), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Investigating CADRs is a diagnostic challenge, with a lack of standardization and significant variability in methodological approaches and clinical practice internationally.^{1,2} Currently available diagnostic tools include drug patch testing, delayed-reading intradermal tests (IDTs), *in vitro* assays, and provocation studies.² Drug patch testing has been suggested to have clinical utility in the identification of the causative drug;³ however, studies evaluating this are generally limited in number and scope, with few detailed prospective reports^{1,4,5} and no studies from the United Kingdom.

The objective of this prospective study was to use quality improvement (QI) methodologies to incorporate patch testing into standard practice for the investigation of CADR and subsequently evaluate the safety, efficacy, and diagnostic capability of drug patch testing. We also conducted a concordance analysis between patch testing and IDT (our center's prior conventional *in vivo* test for CADR) to assess their degree of agreement.

This prospective single center study was conducted at the Department of Adult Allergy, Guy's Hospital, London, UK, and included patients with suspected CADRs as defined by phenotype classification guidelines and scoring systems.⁶ The QI intervention included the distribution of a new flowchart and guideline on investigating CADR in both printed poster and electronic format, in addition to educational sessions on drug patch testing. The outcome measure was number of patients who successfully had drug patch testing performed. This prospective study received full institutional approval as a Quality Improvement Project (LifeQI registration: 110278).

After implementation of the QI intervention we then prospectively studied over a 12-month period (October 2017 to October 2018) all referred patients who underwent drug patch testing for CADR. Patch testing was undertaken at least 6 weeks

after resolution of the original drug eruption and was conducted in accordance with ESCD guidelines⁷ by a patch test trained allergist. Patch testing was performed using IQ-Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) applied for 48 hours and read at day 2 and day 4 as per International Contact Dermatitis Research Group (ICDRG) criteria (with adjustments for lesional FDE studies).⁷ We used allergens from the CADR series (Chemotechnique Diagnostics) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) for over 70% of the patients, and where unavailable, we used the commercialized forms of the drugs prepared (in-house) by diluting to 30% in petrolatum. Delayed-reading IDT was also conducted where appropriate, to aid with a comparative/concordance analysis and was performed at least 6 weeks after resolution of the drug reaction by injecting 0.02 to 0.05 mL of the commercially available drug with readings at 24 and 48 hours, as described in European guidelines.^{7,8} Healthy controls were used for both forms of *in vivo* testing when nonstandardized drugs were tested, to exclude false positive irritant reactions. Provocation studies were also performed where deemed safe and appropriate (ie, negative *in vivo* test) and typically involved a single supervised therapeutic dose administration, followed by a 3-day delayed course (as per UK national guidelines³).

Data were prospectively collected, and categorical data were compared using Fisher's exact test. Cohen's kappa coefficient was used to access concordance between the IDT and patch testing. A *P* value of <.05 was considered significant. Analyses were performed using SPSS Statistics version 20 (IBM Corporation, Armonk, NY).

No patients underwent patch testing for CADR in the 12 months preintervention; however, after the QI intervention this was significantly increased, with a total of 45 patients undergoing drug patch testing (Outcome Measure = 0 vs 45, *P* < .001). Of the 45 patients who underwent patch testing, their ages ranged from 18 to 77 years (mean $\pm$ standard deviation, 45.2 $\pm$ 17.5 years) and 71.1% (*n* = 32) were female and white British was the most common ethnic group tested (82.2%). The most frequently tested CADR phenotype was MPE (*n* = 33), followed by DRESS (*n* = 4), FDE (*n* = 4), AGEP (*n* = 3), and SJS/TEN (*n* = 1). Antibiotics were the culprits most frequently suspected (*n* = 38), and amoxicillin was individually the most commonly patch tested drug (*n* = 11) (Table I).

Overall, drug patch testing was positive in 10 of 45 patients (22.2%), and Table II details these positive cases including cross-reactivity detected. Given the small sample size of CADR cases that underwent patch testing for FDE, DRESS, AGEP, and SJS/TEN, we therefore predominantly focused on conducting a more detailed data analysis (ie, for sensitivity assessment) on the 33 MPE cases, to derive more meaningful diagnostic conclusions regarding drug patch testing. The same applied to the 38 cases with antibiotics implicated, because the number of other drug culprits was considerably smaller. Individual frequencies (*n*) of positive patch test cases for all CADR phenotypes and drug culprits are however provided in Table I.

For MPE, 12.1% of cases (4 of 33) were positive on patch testing and β -lactams were the causative agents in 3 of 4 cases. Patch testing was positive in 8 of 38 (21.1%) suspected antibiotic

TABLE I. Patch test reactivity according to CADR phenotype and drug culprit

CADR phenotype	CADR cases (n)	Positive patch test cases (n)
MPE	33	4
FDE	4	2
DRESS	4	3
AGEP	3	1
SJS/TEN	1	0
Total	45	10

Drug culprit*	Suspected cases (n)	Positive patch test cases (n)
β -Lactams	16	6
Amoxicillin	11	4
Benzylpenicillin	1	1
Clavulanic acid	1	1
Cephalexin	1	0
Meropenem	1	0
Flucloxacillin	1	0
Non- β -lactams	22	2
Clindamycin	3	1
Chloramphenicol	1	1
Metronidazole	2	0
Clarithromycin	3	0
Erythromycin	2	0
Doxycycline	2	0
Ciprofloxacin	1	0
Gentamicin	2	0
Vancomycin	2	0
Rifampicin	1	0
Nitrofurantoin	1	0
Teicoplanin	1	0
Lymecycline	1	0
Antifungal	2	1
H ₂ -receptor antagonists	2	1
Chlorhexidine (biguanide)	1	1
NSAIDs and analgesics	5	0
DMARD	3	0
Antiestrogen	2	0
Nasal decongestant	2	0
Proton pump inhibitor	1	0
Antiepileptic	2	0
Antidepressant	1	0
Xanthine oxidase inhibitor	1	0
Antiviral	1	0
Diuretic	1	0
Benzodiazepine	1	0

AGEP, Acute generalized exanthematous pustulosis; CADR, cutaneous adverse drug reaction; DMARD, disease modifying antirheumatic drug; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; H₂, histamine-2; MPE, maculopapular exanthema; NSAID, nonsteroidal anti-inflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*Multiple drug culprits (>1) were suspected in 17 of 45 patients (37.8%).

CADR cases overall. The reactivity was higher for β -lactams with 37.5% positive patch tests (6 of 16 cases) versus non- β -lactams with 9.1% positive (2 of 22 cases). Amoxicillin was the most frequently positive antibiotic agent with 10.5% reactivity (4 of

38 cases) (Table I). One case of DRESS with multiple antibiotic culprits (amoxicillin and clindamycin) was also detected on patch testing (Table II).

Delayed-reading IDTs were conducted (using the same implicated drugs) in 26 of 45 patients who underwent drug patch testing and 9 positive IDT cases were detected (see Table E2 in this article's Online Repository at www.jaci-inpractice.org for detailed IDT data for the whole cohort). In total, 8 of 26 patients were positive to both IDT and patch testing, and 17 patients gave negative results with both tests. Only 1 discordant test result was reported (positive IDT to vancomycin/teicoplanin with negative patch tests, in an MPE case). Cohen's kappa value was 0.91 (96.2% agreement, $P < .001$).

Of the 33 patients with MPE, 4 patients were positive on both patch and IDT, with 1 patient positive on IDT only (5 in total positive on skin testing) and thus 28 patients were negative on patch and/or IDT (where performed). Challenge tests were conducted on 20 of 28 patients with negative skin tests, and the remaining 8 patients either declined or did not attend their appointments. In total, there were 3 positive (15%) and 17 negative (85%) challenge studies for MPE CADR phenotype (see Table E3 in this article's Online Repository at www.jaci-inpractice.org for details of all MPE cases and test results). Healthy control subjects were all negative on patch or intradermal testing (where required). Two patients suffered moderate flare reactions after IDT (MPE due to chloramphenicol [1:10 dilution] and AGEP due to amoxicillin [1:10 dilution]). No systemic flare reactions from drug patch testing were encountered.

Incorporating prior published patch test specificity data,⁹ our patch test and IDT results, alongside provocation test outcomes and healthy control data, the sensitivity of drug patch testing for the MPE phenotype was calculated at 25%. The sensitivity of drug patch testing with antibiotics was however higher at 36.4%, and on subanalysis it was highest with β -lactams (sensitivity 54.5%) versus non- β -lactams (sensitivity 18.2%) (see Table E4 in this article's Online Repository at www.jaci-inpractice.org for sensitivity calculations).

Here we report the first prospective study on patch testing for CADR that utilized QI methodologies to incorporate drug patch testing into standard practice. Drug patch testing overall had a sensitivity of 25% (for the MPE phenotype), excellent concordance with IDT (96.2% agreement), and a more favorable safety profile, which are novel findings that have not been demonstrated together previously in a prospective report to our knowledge. A recent prospective multicenter study⁴ interestingly reported an overall sensitivity of 56.7%, considerably higher than other published studies^{3,5} and our own results, although the report predominately focused on severe cutaneous adverse reaction phenotypes. This does highlight the variability in patch testing amongst certain CADR.

Patch testing with β -lactam antibiotics had more favorable sensitivity data (54.5%), a finding that mirrors a recent prospective study from Israel.⁵ This further exemplifies how the actual drug(s) implicated strongly influences patch testing usefulness and sensitivity.⁴ However, it is important to note from our study that 7 different drug types were positive on patch testing (ie, penicillins, histamine-2-receptor antagonist, antifungal, β -lactamase inhibitor, lincosamide, biguanide agent, chloramphenicol), which also highlights the necessity of testing all possible culprits (Table II). We also observed 1 case of multiple

TABLE II. Details of positive drug patch test cases and cross-reactivity

Case	Age (sex)	Type of CADR	Drugs patch tested*	Positive drug patch tests	Cross-reactivity detected†
1	25 (F)	MPE	Amoxicillin , benzylpenicillin, aspirin	Amoxicillin	None
2	65 (F)	MPE	Amoxicillin , clavulanic acid , benzylpenicillin	Clavulanic acid	—
3	19 (M)	DRESS	Meropenem , temazepam , spironolactone , ranitidine , cimetidine, rifampicin	Ranitidine, cimetidine	Cimetidine
4	59 (M)	DRESS	Amoxicillin, benzylpenicillin	Benzylpenicillin, amoxicillin	Amoxicillin
5	35 (F)	FDE‡	Fluconazole , itraconazole, voriconazole, ketoconazole	Fluconazole	None
6	69 (M)	AGEP	Amoxicillin , benzylpenicillin	Amoxicillin, benzylpenicillin	Benzylpenicillin
7	42 (F)	DRESS	Amoxicillin , benzylpenicillin, clindamycin , teicoplanin	Amoxicillin, clindamycin	None
8	63 (M)	MPE	Amoxicillin , benzylpenicillin	Amoxicillin	None
9	70 (F)	FDE‡	Chlorhexidine	Chlorhexidine	—
10	43 (M)	MPE	Chloramphenicol	Chloramphenicol	—

AGEP, Acute generalized exanthematous pustulosis; CADR, cutaneous adverse drug reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; F, female; FDE, fixed drug eruption; M, male; MPE, maculopapular exanthema.

*Drugs listed in bold are culprit agents tested and those not in bold (standard) are tested for cross-reactivity purposes.

†Cross-reactivity studies were limited by drug availability and departmental protocol.

‡FDE cases were positive on lesional skin and negative at control skin site (back).

drug hypersensitivity (MDH) linked to DRESS syndrome detected by patch testing. MDH is believed to be related to transient immune suppression, viral reactivation, and possible enhanced immune stimulation to other drug-protein complexes.⁴

Our patch test results also demonstrated excellent agreement with IDT with only 1 discordant result, which is better than a recent prospective study from Australia,¹ whereby only 4 of 9 cases were positive on patch testing, with 5 discordant results. Furthermore, we observed 2 patients developing systemic flare reactions from IDT (despite dilutions) and none with patch testing, although it has been described.⁴ This demonstrates not only improved safety profile with patch testing (although IDT flare reactions are rare) but also their overall comparable diagnostic reliability. Although IDT certainly is a useful tool in diagnosing CADR with reportedly higher sensitivity,¹ patch testing has added benefits in investigating FDE via lesional studies and a distinct advantage when only oral drug preparations are available (ie, for MPE in our study, 14 of 33 cases were appropriate for patch testing only, as the culprit was drug not available as intravenous solution for IDT (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

In conclusion, this prospective study highlights the value of a QI initiative in successfully incorporating drug patch testing into standard practice for the investigation of CADR. Patch testing is also a safe, effective, and useful diagnostic tool and should be considered by more drug allergy centers.

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TABLE E1. Cutaneous adverse drug reaction series used for patch testing

CADR series allergens*	Concentration
Amoxicillin trihydrate	10% pet
Benzylpenicillin	10% pet
Doxycycline monohydrate	10% pet
Erythromycin	10% pet
Clarithromycin	10% pet
Ciprofloxacin	10% pet
Acetylsalicylate acid	10% pet
Paracetamol	10% pet
Clindamycin	10% pet
Cephalexin	10% pet
Ibuprofen	10% pet
Potassium clavulanate	10% pet
Vancomycin hydrochloride	10% aq
Chlorhexidine digluconate	0.5% aq
Gentamicin sulfate	20% pet
Chloramphenicol	5% pet

aq, Aqueous; CADR, cutaneous adverse drug reaction; pet, petrolatum.

*Allergens obtained from Chemotechnique Diagnostics.

TABLE E2. Delayed-reading intradermal test reactivity according to CADR phenotype and drug culprit (including test concentrations)

CADR phenotype	CADR cases (n)	Positive IDT cases (n)
MPE	21	5
DRESS	3	3
AGEP	2	1
Total	26	9

Drug culprit*	IDT dilution [†] (stock solution)	Suspected cases (n)	Positive IDT cases (n)
β-Lactams		15	6
Amoxicillin	Neat (25 mg/mL)	11	4
Benzylpenicillin	1:10 (60 mg/mL)	1	1
Co-amoxiclav	Neat (60 mg/mL)	1	1
Meropenem	1:10 (50 mg/mL)	1	0
Flucloxacillin	1:10 (50 mg/mL)	1	0
Non-β-lactams		17	3
Clindamycin	1:10 (150 mg/mL)	3	1
Chloramphenicol	1:10 (100 mg/mL)	1	1
Metronidazole	1:10 (5 mg/mL)	2	0
Clarithromycin	1:10 (50 mg/mL)	3	0
Erythromycin	1:10 (100 mg/mL)	2	0
Ciprofloxacin	1:100 (2 mg/mL)	1	0
Teicoplanin	1:100 (40 mg/mL)	1	0
Gentamicin	1:100 (40 mg/mL)	2	0
Vancomycin	1:100 (50 mg/mL)	2	1
H2-receptor antagonists (ranitidine)	1:100 (25 mg/mL)	2	1
Chlorhexidine digluconate	1: 2500 (5 mg/mL)	1	0
NSAIDs and analgesics (paracetamol)	1:10 (100 mg/mL)	2	0
Proton pump inhibitor (omeprazole)	1:10 (0.4 mg/mL)	1	0

AGEP, Acute generalized exanthematous pustulosis; CADR, cutaneous adverse drug reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; H2, histamine-2; IDT, intradermal test; MPE, maculopapular exanthema; NSAID, nonsteroidal anti-inflammatory drugs; SCAR, severe cutaneous adverse reaction.

*Multiple drug culprits (>1) were suspected in 16 of 26 patients (61.5%).

†In SCAR cases 10- to 100-fold dilutions of drugs listed for IDT were used instead, to minimize risk of reactivation.

TABLE E3. Maculopapular exanthema cases: skin testing and provocation test outcomes

Case	Patch test performed (Y/N)	Patch test results*	IDT performed (Y/N)	IDT results*	Provocation test performed (Y/N)	Provocation test results
1	Y	Negative AMX , BP	Y	Negative AMX , BP	Y	Negative AMX
2	Y	Negative ERY	Y	Negative ERY	N	—
3	Y	Negative CLIN	Y	Negative CLIN	Y	Positive CLIN
4	Y	Negative ERY , CLIN	Y	Negative CLIN , ERY	Y	Positive CLIN
5	Y	Positive AMX , Negative BP, ASA	Y	Positive AMX , Negative BP	N	—
6	Y	Negative HCQ	N	—	Y	Negative HCQ
7	Y	Positive CLAV , Negative AMX , BP	Y	Positive COA , Negative AMX , BP	N	—
8	Y	Negative AMX , BP, ASA	Y	Negative AMX , BP	Y	Negative AMX , ASA
9	Y	Negative DOX , CIP	Y	Negative CIP	N	—
10	Y	Negative AMX , BP, IBU	Y	Negative AMX	Y	Negative AMX , IBU
11	Y	Negative TOP	N	—	N	—
12	Y	Negative CLR , MET , GEN	Y	Negative CLR , MET , GEN	N	—
13	Y	Negative VANC	Y	Negative VANC	Y	Negative VANC
14	Y	Negative OMP	Y	Negative OMP	Y	Negative OMP
15	Y	Negative MIRT	N	—	Y	Positive MIRT
16	Y	Negative NIT	N	—	Y	Negative NIT
17	Y	Negative TAM	N	—	Y	Negative TAM
18	Y	Negative CIT	N	—	Y	Negative CIT
19	Y	Negative TOP	N	—	Y	Negative TOP
20	Y	Negative CLR	Y	Negative CLR	Y	Negative CLR
21	Y	Negative CLIN	Y	Negative CLIN	Y	Negative CLIN
22	Y	Negative AMX , BP	Y	Negative AMX , BP	N	—
23	Y	Negative LET	N	—	Y	Negative LET
24	Y	Positive AMX , Negative BP	Y	Positive AMX , Negative BP	N	—
25	Y	Negative MES	N	—	N	—
26	Y	Negative DOX	N	—	Y	Negative DOX
27	Y	Negative LYM	N	—	Y	Negative LYM
28	Y	Negative VANC , TEIC	Y	Positive VANC , TEIC	N	—
29	Y	Negative DOX	N	—	Y	Negative DOX
30	Y	Negative CEP	N	—	N	—
31	Y	Negative BP, AMX , FLUC	Y	Negative BP, AMX , FLUC	N	—
32	Y	Positive CLP	Y	Positive CLP	N	—
33	Y	Negative HCQ	N	—	Y	Negative HCQ

AMX, Amoxicillin; ASA, aspirin; BP, benzylpenicillin; CEP, cephalexin; CIP, ciprofloxacin; CIT, citalopram; CLAV, clavulanic acid; CLIN, clindamycin; CLP, chloramphenicol; CLR, clarithromycin; COA, co-amoxiclav; DOX, doxycycline; ERY, erythromycin; FLUC, flucloxacillin; GEN, gentamicin; HCQ, hydroxychloroquine; IBU, ibuprofen; IDT, intradermal test; LET, letrozole; LYM, Lymecycline; MES, mesalazine; MET, metronidazole; MIRT, mirtazapine; N, no; NIT, nitrofurantoin; OMP, omeprazole; TAM, tamoxifen; TEIC, teicoplanin; TOP, topiramate; VANC, vancomycin; Y, yes.

*Bold format = suspected culprit drug(s); normal format = cross-reactive drugs tested.

TABLE E4. Sensitivity of drug patch testing

Drug patch testing variable	True positive*	False negative†	Sensitivity‡
MPE	4	12 (8 DPT not performed, 1 positive IDT, 3 positive DPT)	25%
Antibiotics (all)	8	14 (9 DPT not performed, 1 positive IDT, 4 positive DPT)	36.4%
β-Lactams	6	5 (5 DPT not performed)	54.5%
Non-β-lactams	2	9 (4 DPT not performed, 1 positive IDT, 4 positive DPT)	18.2%

DPT, Drug provocation test; IDT, intradermal testing; MPE, maculopapular exanthema.

*Positive patch tests results were all deemed true positive, based on prior published specificity data^{E1} and/or healthy control subject patch testing.

†When DPT was not performed, the negative patch testing result were counted as false negative for purposes of sensitivity calculations. Positive IDT meant negative patch testing was deemed false negative and thus DPT was not conducted. Positive DPT also meant negative patch testing result was deemed false negative.

‡Sensitivity calculated as: True Positive/True Positive + False Negative.

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