

Patch testing for cutaneous adverse drug reactions in a paediatric population: A retrospective review

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Non-immediate cutaneous adverse drug reactions (CADRs) are mostly clinical manifestations of a Type IV hypersensitivity reaction.^{1,2} In children, diagnosing CADRs is a common challenge for physicians, as childhood rashes are more often due to viral infections but frequently mimic CADRs.^{1,2} A proper diagnosis and identification of the culprit drug avoids misdiagnosis, therefore, preventing unnecessary drug avoidance or replacement, and guides for potential alternatives reducing morbidity from CADRs.^{1–3} Patch tests (PT) are considered useful for diagnosing non-immediate CADRs, however, few paediatric studies have been published.^{2–6} This may be related to the lower incidence of CADRs in children, the lack of PT

standardization especially for severe cutaneous adverse reactions (SCARs) and controversies on PT safety, particularly in this population.^{3–5,7} This study aimed to evaluate the sensitivity and safety of PT for paediatric CADRs.

1 | METHODS/MATERIALS

We conducted a retrospective review of paediatric patients with suspected CADRs who were patch tested at the Dermatology Department of Coimbra University Hospital, over 11 years (2010–2021). The

TABLE 1 Demographics of paediatric with suspected CADR referred for drug patch testing

Characteristic	Total	Drug patch testing	
		Positive	Negative
N, n (%)	22 (100.0)	4 (18.2)	18 (81.8)
Sex (female), n (%)	11 (50.0)	1 (9.0)	10 (91.0)
Age (years), median (IQR)	13.5 (10.0–16.0)	8.0 (4.0–14.0)	14.0 (10.0–16.0)
Atopy, n (%)	5 (22.7)	1 (20.0)	4 (80.0)
Suspected diagnosis			
MPE, n (%)	17 (77.2)	2 (11.8)	15 (88.2)
DRESS, n (%)	3 (13.6)	1 (33.3)	2 (66.7)
SJS, n (%)	1 (4.5)	0 (0)	1 (100)
SJS/TEN overlap, n (%)	1 (4.5)	1 (100)	0 (0)
Time between reaction and patch testing (months), median (IQR)	4 (3.0–6.0)	4 (4.0–4.0)	4 (3.0–12.0)
Reactivation of skin lesions or patch test complications	0 (0)	0 (0)	0 (0)

Abbreviations: CADR, cutaneous adverse drug reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; IQR, interquartile range; MPE, maculopapular exanthem; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

TABLE 2 Individual characteristics of paediatric patients with suspected CADRs referred for patch testing

Patient	Age	Sex	Suspected diagnosis	Suspected culprit drugs	Treatment days till reaction	Clinical situation	Time until testing (months)	Positive allergens			Additional outcomes	Primary diagnosis
								Tested series	Drugs series	Baseline series		
1	4M	MPE	Griseofulvin, oral suspension; Topical tioconazole solution;		2	<i>Tinea capitis</i>	4	BS, SD	Tioconazole	Neomycin sulphate	-	Not confirmed
2	17M	MPE	Vancomycin, IV; Teicoplanin, IV;		3	Cardiac surgery prophylaxis	3	BS, ATB	Vancomycin	IPBC, MDBGN	-	HS to vancomycin
3	14F	MPE	Flucloxacillin, tablet;		7	Paronychia	4	BS, ATB	Flucloxacillin, Dicloxacillin	-	-	HS to flucloxacillin
4	17F	MPE	Amoxicillin/clavulanic acid, tablet; clarithromycin, tablet;		7	Urinary tract infection	1	BS, ATB	-	-	Tolerated upon re-exposure	Para-infectious eruption
5	13F	MPE	Amoxicillin/clavulanic acid, tablet;		7	Tonsillitis	12	BS, ATB	-	-	Tolerated upon re-exposure	Para-infectious eruption
6	17M	MPE	Amoxicillin/clavulanic acid, tablet;		3	CMV infection	2	BS, ATB	-	-	Tolerated upon re-exposure	Para-infectious eruption
7	16M	MPE	Amoxicillin/clavulanic acid, tablet; ibuprofen, tablet;		4	Tonsillitis	3	BS, ATB, NS	-	-	Tolerated upon re-exposure	Para-infectious eruption
8	11F	MPE	Amoxicillin, tablet;		2	Tonsillitis	12	BS, ATB	-	Amerchol L101	Tolerated upon re-exposure	Para-infectious eruption
9	13F	MPE	Amoxicillin, tablet;		6	Tonsillitis	22	BS, ATB	-	-	Tolerated upon re-exposure	Para-infectious eruption
10	14M	MPE	Amoxicillin, tablet; ibuprofen, tablet;		7	Tonsillitis	3	BS, ATB, NS	-	-	Tolerated upon re-exposure	Para-infectious eruption
11	16F	MPE	Cefatrizine, tablet; naproxen, tablet;		9	Joint pain	16	BS, ATB, NS	-	Formaldehyde	Tolerated upon re-exposure	Not confirmed
12	5M	MPE	Etanercept, IV;		42	Juvenile idiopathic arthritis	4	BS, SD	-	Methylisothiazolinone	-	Not confirmed
13	15F	MPE	Co-trimoxazole, tablet; alpha-amylase, tablet;		7	Urinary tract infection	6	BS, ATB, SD	-	Neomycin sulphate	-	Not confirmed
66	17M	MPE	Co-trimoxazole, tablet;		7	Sinusitis	12	BS, ATB	-	-	-	Not confirmed
15	9F	MPE	Oxcarbazepine, oral suspension;		28	Epilepsy	2	BS, AED	-	-	-	Not confirmed
16	10M	MPE	Eslicarbazepine acetate, tablet;		21	Epilepsy	1	BS, AED	-	-	-	Not confirmed
17	10F	MPE	Lamotrigine, tablet;		7	Epilepsy	3	BS, AED	-	-	-	Not confirmed
18	8M	DRESS	Oxcarbazepine, oral suspension;		20	Epilepsy	4	BS, AED	Carbamazepine	-	-	HS to Oxcarbazepine
19	17M	DRESS			21	Acne vulgaris	4	BS, ATB, NS	-	-	-	Not confirmed

TABLE 2 (Continued)

Patient	Age	Sex	Suspected diagnosis	Suspected culprit drugs	Treatment days till reaction	Clinical situation	Time until testing (months)	Positive allergens			Additional outcomes	Primary diagnosis
								Tested series	Drugs series	Baseline series		
20	10F		DRESS	Minocycline, capsule; azithromycin, tablet; nimesulide, tablet;	14	Brain tumour	4	BS, AED	-	-	Skin biopsy suggesting DRESS	DRESS
21	16F		SJS	Amoxicillin/clavulanic acid, tablet; ibuprofen, tablet;	7	Urinary tract infection	6	BS, ATB, NS	-	Thiomersal	-	Not confirmed
22	4M		SJS/TEN overlap	Ethosuximide, capsule;	14	Epilepsy	5	AED, SD	Ethosuximide	-	-	HS to ethosuximide

Abbreviations: ACD, allergic contact dermatitis; AED, antiepileptic drugs series; ATB, antibiotic series; BS, baseline series; CADR, cutaneous adverse drug reaction; CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; HS, hypersensitivity reaction; IPBC, iodopropynyl butyl carbamate; IV, intravenous; MDBGN, methylidibromo glutaronitrile; MPE, maculopapular exanthem; NS, NSAIDs series; SD, suspected drug not included in drug series; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

suspected culprit and related drugs were patch tested mostly at 10% in pet., according to ESCD recommendations, and as in previous studies reported from our department.^{6,8} Details of drug series haptens, chambers and readings are presented in the Supporting Information S1.

2 | RESULTS

We evaluated 22 patients with CADRs (50% female, median age 13.5 years, range 10–16), 17 (77%) with maculopapular exanthemas (MPE), whose main suspected culprits were antibiotics (70%, out of them, 75% beta-lactams), and 5 patients (23%) with SCARs (3 with Drug reaction with eosinophilia and systemic symptoms (DRESS) and 2 in the spectrum of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), 3 related with antibiotics and 2 with anticonvulsants. Non-steroidal anti-inflammatory drugs and/or alpha-amylase were suspected culprits in combination with other drugs in six cases (27% of cases). PT were positive in 2 of 17 (12%) MPE (to vancomycin and flucloxacillin), and in 2 of 5 (40%) SCARs (to carbamazepine in DRESS induced by oxcarbazepine and to ethosuximide in SJS/TEN overlap). Cross-reactivity was observed in two patients, with flucloxacillin and dicloxacillin, and with carbamazepine and oxcarbazepine. A secondary diagnosis of allergic contact dermatitis was confirmed in two cases, one from tioconazole and one from methylisothiazolinone. No adverse reactions occurred during PT. Following recommendations, the patients with a benign MPE possibly provoked by beta-lactams, but with negative PT, were still allowed the re-intake of these drugs, which were eventually well-tolerated by accidental re-exposure, or by formal drug challenges in 8/8 patients.¹ Patients with MPE and negative PT to highly suspected culprits other than beta-lactams were indicated to avoid the possible culprit and alternative drugs were advised. In SCARs, out of precaution, it was advised avoidance of all potentially suspected culprits and structurally related drugs. Both patients with positive PT to carbamazepine and ethosuximide tolerated levetiracetam and valproate (non-aromatic anticonvulsants). Demographics and individual characteristics of patients and PT results are summarized in Tables 1 and 2.

3 | DISCUSSION

Although the number of patients in our sample is small, their clinical characteristics indicate that children with severe or highly suspected mild CADRs were the ones tendentially referred for PT, as in other studies.⁵ PT positivity rate was similar to the literature, indicating an overall low sensitivity and a widely variable sensitivity depending on the clinical presentation and the culprit drugs.^{4,5} Exanthema from other causes, such as infections or complex interactions between drugs and virus are pointed as one of the main reasons for the low PT sensitivity in MPE.^{1,6,9,10} Regarding SCARs, the sensitivity is related mainly to the involved drugs (higher with anticonvulsants) and because the probability of a positive PT increases with the severity of the CADRs, as shown in several studies.^{5,7,9}

As in adults, in this paediatric population PT were safe and a significant percentage of patients confirmed the culprit and suggested potentially safer alternatives in SCARs, particularly to anticonvulsants.^{2,6} Due to the relatively low sensitivity of PT in suspected MPE to beta-lactams, PT does not fully replace drug provocation tests (DPTs), which are considered the gold standard diagnostic tool in these cases.^{1,3,6} Similarly, intradermal tests have low sensitivity, and together with the difficulty of performing painful tests in children, several studies recommend a direct DPT in 'benign CADRs'.³ For drugs other than beta-lactams, there is some controversy on a direct DPT.^{2,4,6} Apart from being time-consuming when more than one culprit is suspected, DPT are contraindicated in SCARs. Therefore, we can recommend PT as a safe first step in the study of non-immediate CADR, particularly from drugs other than beta-lactams, but more studies are needed to establish PT sensitivity in the paediatric population.

AUTHOR CONTRIBUTIONS

Jóni Carvalho: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); writing – original draft (lead); writing – review and editing (equal). **Iolanda Alen Coutinho:** Conceptualization (equal); investigation (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Ana Luísa Matos:** Investigation (supporting); resources (supporting); visualization (supporting). **Pedro Alves:** Data curation (supporting); investigation (supporting). **Leonor Ramos:** Data curation (supporting); investigation (supporting); resources (supporting). **Margarida Gonçalves:** Conceptualization (supporting); formal analysis (lead); investigation (lead); resources (supporting); supervision (equal); validation (supporting); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting).

CONFLICT OF INTEREST

Margarida Gonçalves provided lectures and advisory boards for AbbVie, Leo, Lilly, Novartis, Pfizer, Sanofi and Takeda. The other authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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