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A Pediatric Case of Selective Fixed Drug Eruption to Amoxicillin

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Clinical implications: We report the first case of classical fixed drug eruption selective to amoxicillin in the pediatric setting. Our case highlights the importance of drug provocation test in diagnosing this entity, and that cross-reactivity to similar molecules might be absent.

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Abbreviations: Benzylpenicillin (BP), Drug provocation test (DPT), Fixed drug eruption (FDE), Penicilloyl-polylysine (PPL)

To the Editor:

Background:

Fixed drug eruption (FDE) is a distinctive type of delayed drug hypersensitivity that presents with dermal inflammation of limited involvement recurring at the same location upon exposure to the culprit drug. It is typically characterized by an erythematous single lesion with sharp margins, even though multiple-site involvement can also occur. Appropriate testing to confirm diagnosis is still debated, although graded drug provocation test (DPT) seems to be more sensitive (1). Drugs most frequently associated with FDE include analgesics, antimalarials, barbiturates and antibiotics, including amoxicillin (2, 3). However, the evaluation of cross-reactivity of the culprit drug to others agents with similar chemical structure has been poorly studied. We present here a rare case of FDE to amoxicillin reproducible with a DPT in which we also assessed cross-reactivity with other beta-lactams both with and without identical lateral chains.

Methods:

Skin prick tests were performed on the volar forearm of the patient with penicilloyl-polylysine (PPL) 6.0×10^{-5} M (PRE-PEN®, AllerQuest, LLC, Plainville, USA),

benzylpenicillin (BP) 10 000 IU/mL (Fresenius Kabi Canada Ltd, Richmond Hill, Canada) and amoxicillin 50 mg/mL (Teva Canada Limited, Toronto, Canada). Intradermal testing was performed with PPL 6.0×10^{-5} M and BP 10 000 UI/mL. Intradermal testing was not performed with amoxicillin since an injectable form or commercially distributed reagent is not available in North America.

Patch tests were performed and interpreted after 24 and 48 hours according to the European Society of Contact Dermatitis guidelines (4). Extra and intralesional patch testing with penicillin V potassium and amoxicillin were performed at a 30 percent dilution in a petrolatum vehicle using Finn chambers (Smartpractice, Phoenix, USA). A skin biopsy was offered to the patient and his parents but, considering the invasiveness of the procedure and the lack of therapeutic benefits, the consent was not obtained.

The patient also underwent successive DPT to amoxicillin (45 mg/kg), penicillin V potassium (25 mg/kg) and cefprozil (15 mg/kg) in the allergy outpatient clinic with an interval of 4 to 6 weeks between the different tests. DPT consisted of a graded oral challenge starting at 1/100 of the total antibiotic dose, 1/10 of the dose 30 minutes later, followed by full dose after an additional 30 minutes if no reaction was noted. When negative, each DPT was followed by a four-day home DPT with the concordant agent to assess for delayed-type reactions.

Results:

We report a case of a healthy 4-year-old boy who presented with a clinical picture compatible with FDE to amoxicillin. His personal history was only significant for mild asthma. Well-demarcated pruriginous oval lesions on the right base of the neck, the anterior thorax, and the inner right thigh appeared on the second day of amoxicillin treatment for an otitis media in 2014. About a year later, three identical lesions reappeared 24 hours after being re-exposed to amoxicillin that had been prescribed for bronchitis. The lesions lasted a week after amoxicillin discontinuation.

During his initial evaluation at the outpatient allergy clinic, skin prick tests to PPL, BP, and amoxicillin were negative with a positive histamine control. Intradermal skin tests to PPL and BP were also negative. Patch tests to amoxicillin and penicillin V potassium on both the resolved cutaneous lesion on the neck and on healthy skin on the back were negative at 48 and 72 hours (Figure 1A).

Amoxicillin DPT was positive 4 hours after exposure with a recurrence of the three lesions at the same initial locations (Figure 1B). The lesions resolved within two days with topical corticosteroid treatment of mild potency. Subsequent DPT with penicillin V and cefprozil were performed 4 to 6 weeks later and were negative, including the four-day home DPT.

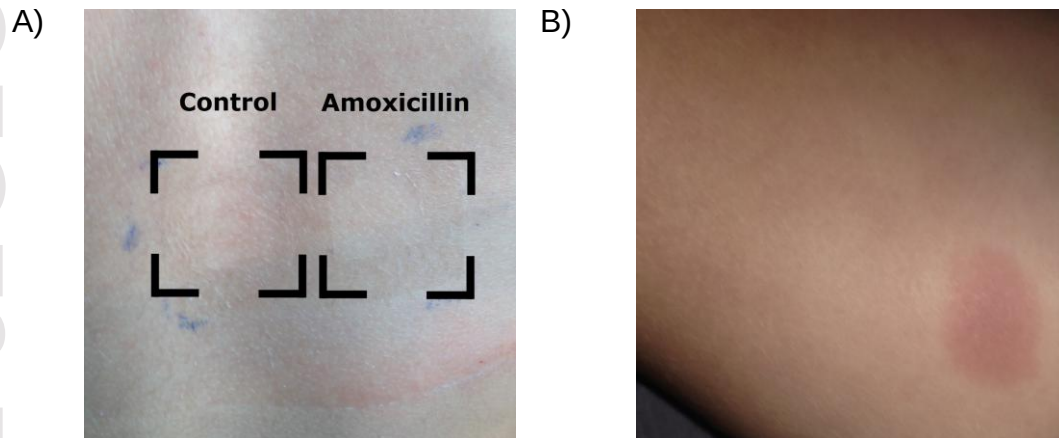


Figure 1. A) Negative patch testing B) Recurrence of the skin lesion of the inner thigh following drug provocation test

Discussion:

FDE is a unique local reaction to drugs that can occur in all age groups. In children, it is estimated to occur in less than 15% of cutaneous adverse drug reactions (5). The underlying immunologic mechanism behind this unusual reaction is thought to be mediated through intraepidermal CD8⁺ T cells with an effector-memory phenotype. Upon activation via the CD3-TCR complex, these T cells residing in the resting lesions display cytolytic activity against keratinocytes, producing IFN- γ and cytotoxic granules in part responsible for the localized epidermal damage (6). In accordance with the extended Gell and Coombs classification modified by Pichler (7), FDE thus falls into a type IVc hypersensitivity reaction in which cytotoxic T cells are key effectors in mediating the associated cutaneous disease.

To our knowledge, no classical FDE selective to amoxicillin has been described in the pediatric population, although it has occasionally been seen in adults. Pediatric cases previously described in association with amoxicillin are depicted in Table 1. Özkaya *et al.* report the case of a 12-year-old that presented with an amoxicillin-induced rash with overlapping features of symmetrical drug-related intertriginous and flexural exanthem (SDRIFE), also known as baboon syndrome, and possible FDE (8). A rare mucosal FDE confined to the tongue has been described by Dhar *et al.* in a 4-year-old (9). More recently, an atypical penile non-pigmenting FDE to amoxicillin has been diagnosed in a 10-year-old boy (10). Finally, in an international retrospective study of 35 pediatric patients with FDE, amoxicillin was found to be causative in one 11-year-old female patient, although this patient did not undergo confirmatory challenge testing (11). Our patient would appear to be the first to present typical amoxicillin-induced multiple FDE lesions at such a young age.

With regards to diagnostic evaluation, skin testing was negative in our patient, including skin prick testing and intradermal testing to the available reagents. Intralesional and extralesional patch testing was also negative, suggesting that the sensitivity of skin testing is limited in this condition, and that DPT remains the gold standard and a safe method for making the diagnosis of FDE. This is consistent with Barbaud's findings that patch testing yields poor results in antibiotic-mediated FDE (1).

Table 1. Pediatric cases of FDE to amoxicillin previously described

Source	Number of patients	Age (years) and sex	Drug involved	Description	Single or multiple lesions	Assessment of selectivity
Özkaya <i>et al.</i> (8)	n = 1	12, M	Amoxicillin	Overlapping features of SDRIFE and FDE	Single	No
Dhar <i>et al.</i> (9)	n = 1	4, M	Amoxicillin	Mucosal FDE of the tongue	Single	No
Keli-Bhija <i>et al.</i> (10)	n = 1	10, M	Amoxicillin	Penile non-pigmenting FDE	Single	Partially
Morelli <i>et al.</i> (11)	n = 1	11, F	Amoxicillin	FDE of the arm	Single	No, no confirmatory challenge

Abbreviations: F, female; FDE, fixed drug eruption; M, male, SDRIFE, symmetrical drug-related intertriginous and flexural exanthem

Moreover, we have also assessed cross-reactivity to other penicillins with penicillin V potassium DPT, as well as tolerability to cephalosporins with similar lateral chains such as cefprozil, indicating a true selective hypersensitivity reaction to amoxicillin (Figure 2). Selective antibiotic allergy has been described in other hypersensitivity reactions such as IgE-mediated allergy, but we are the first to report an absence of reaction to molecules with similar lateral chains in a pediatric patient with FDE. Indeed, the only other case in the pediatric literature that assessed tolerability to other beta-lactams performed challenges with penicillin V and cefuroxime, a third generation cephalosporin that does not share its lateral chain with amoxicillin (10). Therefore, it appears that none of the amoxicillin-induced FDE cases previously mentioned have thoroughly assessed cross-reactivity. This finding is of crucial importance, since children labeled with this

complex hypersensitivity reaction might not need to avoid all beta-lactams, not even molecules with identical lateral chains, thus insuring a greater choice of future antibiotic use if needed. Perhaps this selectivity can be explained by a different three-dimensional epitope presentation depending on specific drug molecular characteristics.

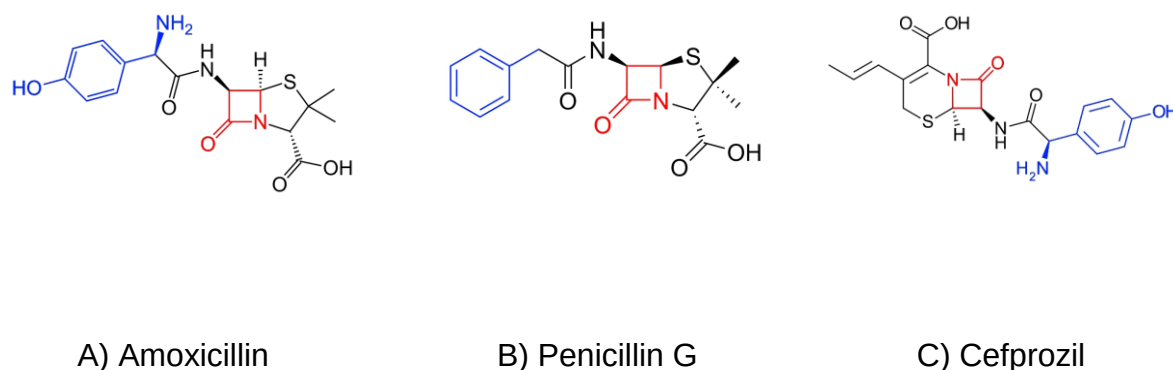


Figure 2. Illustration of allergy selectivity

Conclusion:

We describe here the first pediatric case of a classic FDE entirely selective to amoxicillin tolerating penicillin V potassium and cephalosporins with identical lateral chains. Moreover, our case strengthens the idea that DPT is the most reliable test for FDE diagnosis.

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