

CORRESPONDENCE

Cross-reactivity to penicillins in cephalosporin anaphylaxis

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Keywords: anaphylaxis; cephalosporin allergy; drug allergy; drug hypersensitivity; drug provocation testing; penicillin allergy; perioperative anaphylaxis; skin testing

Editor—Beta-lactam antibiotics are a leading cause of perioperative anaphylaxis in Australia and the UK.^{1,2} Cephalosporins, particularly cefazolin, are recommended first-line antibiotics for prevention of surgical site infections in Australia.³ There is no clear consensus whether there is clinically significant cross-reactivity between penicillins and cephalosporins. Although exact antigenic determinants of cephalosporins are not known, cross-reactivity is probably mainly determined by the R1-side chain.^{4,5} Cefazolin has a different R1-side chain to other penicillins and cephalosporins. Case series observe negative penicillin skin testing (PST) and tolerance to penicillins and other cephalosporin^{4–7} in patients with cefazolin anaphylaxis.

Cross-reactivity may also occur through immunoglobulin E (IgE) antibodies that recognise neodeterminants of the common beta-lactam ring structure.^{5,8} Small numbers of patients with cefazolin anaphylaxis have positive PST⁵; therefore, current recommendations by the American Academy of Allergy Asthma and Immunology (AAAAI) and British Society for Allergy and Clinical Immunology (BSACI) suggest PST followed by penicillin drug provocation testing (DPT) after a diagnosis of cefazolin anaphylaxis.^{8,9} After negative DPT, penicillins can be prescribed.^{4,9} We assessed the safety and feasibility, in patients with cephalosporin anaphylaxis, of penicillin DPT without PST in the evaluation of cross-reactivity to penicillins.

We recruited patients sequentially from the Anaesthetic Allergy Clinic (AAC), Royal North Shore Hospital, Australia, between January 1, 2018 and June 30, 2019, with IgE-mediated cephalosporin anaphylaxis (Trial registry: LNR/16/HAWKE/452). Patients received standard assessment comprising review of clinical history including prior history of penicillin or cephalosporin allergy, intradermal testing (IDT) to all drugs and substances administered before the onset of anaphylaxis, serum tryptase levels (ImmunoCAP; ThermoFisher, Uppsala, Sweden), and specific IgE (sIgE) to morphine, pholcodine, latex,

and chlorhexidine where clinically relevant. IDT was performed per Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) guidelines and classified as positive if the wheal doubled in size or increased by 3 mm at any testing concentration.¹

Patients were diagnosed with IgE-mediated cephalosporin anaphylaxis based on suggestive clinical history supported by elevated mast cell tryptases, positive IDT to the culprit cephalosporin, and negative IDT to other drugs and substances tested.

IDT skin testing to cephalosporins was performed at both the initial and suggested maximum concentrations published in ANZAAG guidelines.¹ PST was performed where anaphylaxis was to a cephalosporin other than cefazolin, or where, not including the current episode of cephalosporin anaphylaxis for review, there was a history of anaphylaxis to penicillins or cephalosporins at any time point, or a history of reaction to penicillins or cephalosporin in the 12 months before the review.¹⁰ PST was performed using benzylpenicillin, amoxicillin, Diater PPL® (benzylpenicilloyl-polysine), and Diater MDM® (minor determinant mixture) (Diater Laboratories, Madrid, Spain) at two serial concentrations as per Australian Society of Clinical Immunology and Allergy Guidelines.¹¹

All patients with negative PST or no or 'low risk' penicillin or cephalosporin allergy histories received direct DPT to amoxicillin, administered via a three-step protocol, that is 1% of target dose followed by 10% of target dose and finally the full target dose (500 mg or adjusted for renal failure). Patients were then prescribed a 3-day course of amoxicillin.

Forty-four of 256 patients reviewed during the study period had IgE-mediated cephalosporin anaphylaxis, 40 had anaphylaxis to cefazolin, two to cefalotin, and two to ceftriaxone (Table 1). All 44 patients completed a 3-day amoxicillin challenge with no immediate adverse reaction reported. One

Table 1 Clinical characteristics of 44 patients with cephalosporin anaphylaxis. *Peak tryptase levels were not performed in six patients. †One patient reported a benign delayed rash beyond 12 months of review.

Patients, n	44
Age, yr, median (range)	51 (13–87)
Female, n (%)	25 (57)
Significant increase and decrease in tryptase, n (%)	35 (92)*
Prior drug allergy history to penicillins or cephalosporins, n (%)	1 (2)†
Cephalosporin exposed to	
Cefazolin	40
Skin test positive to cefazolin at 1 mg mL ⁻¹	30
Skin test positive to cefazolin at 10 mg mL ⁻¹	40
Skin test negative to cefazolin	0
Cefalotin	2
Skin test negative to cefazolin	2
Ceftriaxone	2
Skin test negative to cefazolin	2
System involved	
Cardiovascular only	26
Respiratory	2
Cardiovascular and respiratory	16
Skin involvement	24
Category of anaphylaxis	
Not life threatening	6
Life threatening	36
Cardiac or respiratory arrest	2

patient reported a delayed benign rash at 24 h and ceased amoxicillin.

Our data comprising 40 patients with cefazolin anaphylaxis with no adverse reaction to a 3-day amoxicillin challenge builds upon smaller cohorts reported recently.^{5,7} No patients reported a history of penicillin or cephalosporin allergy that required PST. Pipet and colleagues⁵ reported 10 patients with cefazolin anaphylaxis supported by either positive skin testing at 2 mg mL⁻¹, or challenge. Eight patients were challenged to, and tolerated, amoxicillin or cefuroxime. One patient had positive skin tests to amoxicillin, ampicillin, cefuroxime, and cefotaxime, and did not proceed to DPT. Uyttebroek and colleagues⁷ reported 36 patients with possible cefazolin anaphylaxis with 19 demonstrating sensitisation on PST, 12 at the standard concentration of 2 mg mL⁻¹, and seven at 20 mg mL⁻¹. All 16 patients who attended subsequent DPT tolerated penicillin or cephalosporin. Therefore, apart from the one patient reported by Pipet and colleagues⁵ with positive PST who was not challenged, 64 of 65 patients in three recent case series with cefazolin anaphylaxis who attended subsequent DPT tolerated penicillins or another cephalosporin. Although cross-reactivity may stem from the common beta-lactam ring structure, 64 of 65 patients did not have such cross-reactivity.

Cross-reactivity in cephalosporin allergy other than cefazolin allergy is more challenging. Identical or similar R1-side chains are present amongst amoxicillin, ampicillin, piperacillin, cephalixin, and cefaclor. Our data in relation to cephalosporins other than cefazolin are small, and therefore we are unable to draw meaningful conclusions without further studies. Our study included two patients with cefalotin

anaphylaxis, and two with ceftriaxone anaphylaxis; all had negative PST and tolerated 3-day amoxicillin challenge.

Combined with two smaller case series,^{5,7} our study suggests that cefazolin allergy may be specific. Patients may be able to tolerate penicillins without the need for further evaluation. However, additional case series are needed before it can be definitively concluded that penicillin DPT and PST are not required after cefazolin anaphylaxis. The benefit conferred from this conclusion when confirmed with further studies will be reduced unnecessary testing, reduced reagent cost, reduction in waiting lists for anaesthetic and drug allergy clinics, and more appropriate perioperative antibiotic prescribing in penicillin allergy-labelled patients.

Declaration of interest

The authors declare that they have no conflicts of interest.

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doi: 10.1016/j.bja.2019.09.011