Sensitization Phenotypes in Immediate Hypersensitivity to Cephalosporins: A Cluster Analysis Study

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Reactions to cephalosporins are increasing owing to the widespread use of these agents [1]. Cephalosporins, particularly cefazolin, are among the most frequent causes of perioperative anaphylaxis [2,3]. Cross-reactivity between cephalosporins and other ß-lactams is constantly evolving. In most cases, cross-reactivity can be explained by identical or similar R1 side chains [4,5]. However, other studies concerning cross-reactivity among ß-lactams found that the risk of developing a reaction does not depend only on the structural similarities between side chains [6,7], thus indicating the possibility of coexisting sensitivity to other drugs in the family.

Hierarchical cluster analysis has been used to identify phenotypes. We postulate that cluster analysis applied to patients with hypersensitivity to cephalosporins could reveal cephalosporin hypersensitivity phenotypes. Therefore, we applied hierarchical cluster analysis to identify phenotypic subgroups.

We retrospectively analyzed patients aged ≥14 years with suspected, immediate allergic reactions to cephalosporin between 1995 and 2019.

Diagnosis of allergy to ß-lactams, including cephalosporins, has been based on our departmental protocol since 1995, with readjustments as successive guidelines were published [5,8]. Briefly, patients with suspected immediate hypersensitivity to ß-lactams are managed based on a medical history and skin tests (STs). STs are performed with penicillin reagents and cephalosporins at recommended nonirritant concentrations [5]. If STs are negative, the patients undergo controlled drug provocation tests (DPTs). If the clinical history is suggestive and more than 6 months have elapsed between reaction and diagnosis, STs and DPTs are repeated 3 weeks later.

Continuous data were summarized as mean (SD), and categorical data as count (%). The analysis was performed using complete linkage clustering. We included 10 variables: sex, age, time from the reaction to the allergy evaluation, culprit cephalosporin, type of reaction, atopy, positive STs with major/minor penicillin determinants, positive STs with amoxicillin, positive STs with the eliciting cephalosporin, and positive STs with other cephalosporins.

Group comparisons were performed using the Fisher exact test with a post hoc Bonferroni adjustment. Statistical analyses were performed using SPSS software, Version 26 (IBM Corp).

Of 178 patients with suspected immediate allergic reactions to cephalosporins, 85 (47.8%) were diagnosed with immediate allergy (Supplementary Fig. 1). Concerning patients with confirmed diagnosis, the mean age was 47.52 (1.79) years (median, 47.5), and 56.5% were female. Second-generation cephalosporins were the most frequently involved cephalosporins, reaching 44.7% of cases, followed by third-generation cephalosporins in 27.1%, first-generation cephalosporins in 27.1%, and fourth-generation cephalosporins in only 1.2%. Concerning reactions, 52.9% of patients had urticaria/angioedema and 47.1% anaphylaxis.

Of 85 patients diagnosed with immediate hypersensitivity, 67 (78.8%) had positive ST results, and 18 (21.2%) had positive DPT results with the suspected cephalosporin. Of the 67 patients with positive STs, 10 (14.9%) had positive ST results with penicilloyl poly-L-lysine/benzylpenicilloyl-octa-L-lysine, minor determinant, or benzylpenicillin, and 8 (11.9%) had positive ST results with amoxicillin (Supplementary Table 1). Fifty-nine patients (69.4%) had positive STs with the suspected cephalosporin, and exclusively with the culprit cephalosporin in 47 cases (55.3%). In 66 patients, cephalosporins other than the eliciting ones were tested. Eleven patients (16.7%) had positive STs with cephalosporins other than that involved. In 8 of the 11 patients, STs were positive with cephalosporins with identical or similar R1 side chains (Supplementary Table 1).

Cluster analysis identified 3 clusters (Supplementary Fig. 2). The clinical characteristics and diagnoses are shown in the Table.

Table. Clinical Characteristics of Clusters

Characteristics	Cluster A (n=25)	Cluster B (n=54)	Cluster C (n=6)
Females, No. (%)	18 (72.0)	26 (48.1)	4 (66.7)
Mean (SD) age, y	49.92 (16.61)	46.47 (16.40)	39.25 (3.326)
Cephalosporins, No. (%)			
Cefazolin	18 (72.0)	0	0
Cephalexin	1 (4.0)	0	0
Cefadroxil	3 (12.0)	0	0
Cefaclor	3 (12.0)	2 (3.7)	0
Cefonicid	0	4 (7.4)	0
Cephalothin	0	0	1 (16.7)
Cefuroxime	0	28 (51.9)	1 (16.7)
Ceftriaxone	0	11(20.4)	0
Cefotaxime	0	5 (9.3)	1 (16.7)
Cefixime	0	3 (5.6)	3 (50.0)
Cefepime	0	1 (1.9)	0
Type of reaction, No. (%)			
Urticaria	17 (68.0)	28 (51.9)	0
Anaphylaxis	8 (32.0)	26 (48.1)	6 (100.0)
Mean (SD) time since reaction to study, mo	26.64 (46.28)	7.37 (19.29)	65.67 (144.45)
Atopy, No. (%)	4 (16.0)	6 (11.1)	1 (16.7)
Positive STs with penicillin determinants, No. (%)	2 (8.0)	5 (9.3)	5 (83.3)
Positive STs with AX, No. (%)	3 (12.0)	2 (3.7)	4 (66.7)
Positive STs with the culprit cephalosporin, No. (%)	15 (83.3)	41 (78.8)	3 (10.0)
Positive STs with other cephalosporins, No. (%)	1 (4.0)	8 (13.8)	2 (50.0)

Abbreviation: AX, amoxicillin; ST, skin test.

Cluster A comprised 25 patients, of whom most were female and 18 experienced reactions to cefazolin. Only 2 patients with reactions to cefazolin had positive STs with penicillins. No patients had positive ST results with other cephalosporins. This cluster could comprise a phenotype with selective hypersensitivity to cefazolin.

In cluster B (n=54), sensitization was mainly to second- and third-generation cephalosporins, with 9.3% and 16.7% sensitized to penicillin determinants and other cephalosporins, respectively. This cluster could constitute second and third cephalosporin hypersensitivity phenotypes.

Cluster C was the least frequent (n=6) and was characterized by the longest time from reaction to study (P=.009). All patients had experienced anaphylaxis (P<.0001). STs with penicillin determinants and amoxicillin were positive in 5 and 4 patients, respectively (P<.0001), and 2 of the 4 patients had positive ST results to other cephalosporins. This cluster could be an extended-sensitization hypersensitivity phenotype.

We evaluated 178 patients with a clinical history of immediate reactions to cephalosporin. Reactions were confirmed in 47.7%. This figure is similar to others published elsewhere [4,9].

The negative predictive value of STs with cephalosporins is not well established; therefore, DPTs with the culprit cephalosporin are recommended to confirm or rule out the diagnosis of allergy [5]. In our study, DPTs confirmed immediate hypersensitivity to cephalosporins in 21.2% of patients, which is similar to findings from other studies [4,10].

Cluster analysis has been used to identify asthma phenotypes [11], chronic rhinosinusitis endotypes [12], and sensitization patterns in atopic children [13]. However, no studies have used multivariate analysis to classify drug hypersensitivity. The present study sought to assess whether different clusters can be identified in patients with immediate hypersensitivity to cephalosporins.

Three clusters were identified (Table). Cluster A included all patients with reactions to cefazolin, of whom about 90% were selective reactors. Several studies have confirmed side chain specificity in patients with immediate hypersensitivity to cefazolin [14]. Cluster B included reactions predominantly due to the second-generation cephalosporin cefuroxime and most reactions to third-generation cephalosporins. Selective sensitization to the suspected cephalosporin was predominant. Sensitization to cephalosporins other than the eliciting cephalosporin seemed related to the similarity of the R1 side chain, as previously described [4,5]. Cluster C included patients with anaphylaxis and positive STs with penicillins and other cephalosporins, possibly owing to cross-reactivity or cosensitization [5]. Furthermore, the time from reaction to study in cluster C was longer than in the other clusters, consistent with the results of a study evaluating the evolution of STs in patients with immediate cephalosporin hypersensitivity [15], in whom patients sensitized to penicillins were most likely to maintain positive ST results. Although the number of patients was small, the cluster included patients with severe reactions.

The main limitations of our study are its retrospective nature and the fact that the cephalosporins tested throughout the study period varied. Prospective studies should be carried out with larger samples. We suggest that better characterization of sensitization clusters could aid in clinical diagnosis and risk stratification.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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