

Sensitization phenotypes in immediate hypersensitivity to cephalosporins: A cluster analysis study

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Reactions to cephalosporins are increasing due to their wide use [1]. Cephalosporins, particularly cefazolin, are among the most frequent causes of perioperative anaphylaxis [2,3]. Cross-reactivity between cephalosporins and other beta-lactams (BL) is a changing issue. In most cases, cross-reactivity can be explained by identical or similar R1 side chains [4,5]. However, other studies concerning cross-reactivity among BLs 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 sensitivities to different BLs.

Hierarchical cluster analysis has been used to identify phenotypes. We postulate that cluster analysis applied to cephalosporin hypersensitivity patients could determine cephalosporin hypersensitivity phenotypes and aimed to apply hierarchical cluster analysis to identify phenotypic subgroups of patients.

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

Allergy work-up

The allergic diagnosis to BLs, including cephalosporins, has been protocolized in our department since 1995, readjusting to successive guidelines [5,8]. Briefly, patients with suspected immediate hypersensitivity to BLs first underwent a medical history and skin

tests (STs). STs were performed with penicillin reagents and cephalosporins using recommended nonirritant concentrations [5]. If STs were negative, the patients underwent controlled drug provocation tests (DPT). If the clinical history was suggestive and more than six months had elapsed between reaction and diagnosis, STs and DPTs were repeated three weeks later.

Statistical analyses

Continuous data were summarized as mean \pm standard deviations, and categorical data were described with count (%) values. Complete linkage hierarchical classification method was utilized to perform cluster analysis. Ten variables were included in the cluster analysis: gender, age, the time elapsed since the reaction to the allergy evaluation, culprit cephalosporin, type of reaction, atopy, positive STs with major/minor penicillin determinants, positive STs with AX, positive STs with the eliciting cephalosporin, and positive STs with other cephalosporins.

Group comparisons were performed with Bonferroni post hoc and Fischer's exact test. Statistical analyses were performed using SPSS software, version 26 (IBM, Armonk, NY).

Of 178 patients evaluated with suspected, immediate allergic reactions to cephalosporins, 85 patients (47.8%) were diagnosed with immediate allergy (supplementary Fig 1). The mean age was 47.52 ± 1.79 years (median 47.5), and 56.5% were females. Second-generation cephalosporins were the most frequently involved cephalosporins, reaching 44.7% of cases, followed by third-generation (28.2%) and first-generation cephalosporins (27.1%). 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 STs, and 18 (21.2%) had positive DPTs with the suspected cephalosporin. Of 67 patients with positive STs, 10 (14.9%) had positive STs with PPL/BP-OL (Penicilloyl poly-L-lysine /Benzylpenicilloyl- octa- l- lysine), MD (minor determinant), or BP (bencylpenicillin); and 8 (11.9%) had positive STs with amoxicillin (Supplementary Table 1). Sixty-four patients (75.1%) had positive STs with the suspected cephalosporin. In 66 patients cephalosporins different than the eliciting ones were tested. Eleven patients (16.7%) had positive STs with other cephalosporins in addition to that involved. In 8 of 11 patients, STs were positive with cephalosporins with identical or similar R1 side chains (Supplementary Table 1). Forty-three patients (65.2%) had positive results exclusively with the culprit cephalosporin.

Cluster analysis identified three clusters (Supplementary Fig. 2). Clinical characteristics and diagnosis results are shown in Table 1.

Cluster A (n=25) had female predominance and included 18 patients with reactions to cefazolin. Only two patients with cefazolin reactions had positive STs with penicillins. No patients had positive STs with other cephalosporins. This phenotype could be a selective cefazolin hypersensitivity cluster.

In Cluster B (n=54), sensitization was to second and third-generation cephalosporins. Sensitization to penicillin determinants and other cephalosporins was 9.3% and 16.7%, respectively. This phenotype could be a second-third cephalosporin hypersensitivity cluster.

Cluster C was the less frequent (n=6). Patients had the longest time from reaction to study (p=0.009). All patients had had anaphylaxis (p<0.0001). STs with penicillin determinants and AX were positive in 5 and 4 patients, respectively (p<0.0001), and also 5 of 6 patients had positive STs to other cephalosporins. This phenotype could be an extended sensitization hypersensitivity cluster.

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

The negative predictive value (NPV) of STs with cephalosporins is not well established; therefore, DPTs with the culprit cephalosporin are recommended to confirm or discard the diagnosis of allergy [5]. In our study, the percentage of patients in which DPTs confirmed immediate hypersensitivity to cephalosporins was 21.2%, figure similar to that reported [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 investigations have been performed using multivariate classification analysis of 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 1). Cluster A included all patients with reactions to cefazolin, of which 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 sensitizations to the suspected cephalosporin were predominant. Sensitization to

cephalosporins, additionally to 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. That could be due to cross-reactivity or co-sensitization [5]. Also, the time elapsed from reaction to study was higher than in the other clusters. That would agree with a study evaluating the evolution of STs in patients with immediate cephalosporin hypersensitivity [15], in which patients sensitized to penicillins were most likely to maintain positive STs. Although the number of patients was small, the cluster included patients with severe reactions.

This study's main limitation is its retrospective nature, with some variations in involved and tested cephalosporins throughout the study time. Prospective studies should be carried out with higher numbers of individuals. We suggest that better characterizing of sensitization clusters could aid in clinical diagnosis and risk stratification.

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Conflict of interest

Authors have no conflict of interest in relation with this manuscript.

References

1. Versporten A, Coenen S, Adriaenssens N, Muller A, Minalu G, Faes C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe (1997-2009). *J Antimicrob Chemother.* 2011;66 Suppl 6:vi25-35.
2. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol.* 2008;18(5):350-6.
3. Gonzalez-Estrada A, Pien LC, Zell K, Wang XF, Lang DM. Antibiotics are an important identifiable cause of perioperative anaphylaxis in the United States. *J Allergy Clin Immunol Pract.* 2015;3:101-5.e1.
4. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montañez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol.* 2006;117:404-10.
5. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. *Allergy.* 2020;75:1300-1315.
6. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med.* 2004;141:16-22.
7. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol.* 2015;136:685-691.
8. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy.* 2003;58:961-72.
9. Yuson C, Kumar K, Le A, Ahmadie A, Banovic T, Heddle R, et al. Immediate cephalosporin allergy. *Intern Med J.* 2019;49:985-993.
10. Romano A, Guéant-Rodriguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP, et al. Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy.* 2005;35:1234-42.
11. Sendín-Hernández MP, Ávila-Zarza C, Sanz C, García-Sánchez A, Marcos-Vadillo E, Muñoz-Bellido FJ, et al. Cluster Analysis Identifies 3 Phenotypes within Allergic Asthma. *J Allergy Clin Immunol Pract.* 2018;6:955-961.
12. Tomassen P, Vandeplass G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol.* 2016;137:1449-1456.
13. Venter C, Maslin K, Zhang H, Kaushal A, Terry W, Patil VK, et al. Use of cluster analysis to characterize patterns of sensitization in childhood allergy. *Pediatr Allergy Immunol.* 2018;29:644-648.
14. Uyttebroek AP, Decuyper II, Bridts CH, Romano A, Hagendorens MM, Ebo DG, et al. Cefazolin Hypersensitivity: Toward Optimized Diagnosis. *J Allergy Clin Immunol Pract.* 2016;4:1232-1236.
15. Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quarantino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy.* 2014;69(6):806-9.

Table 1. Clinical characteristics of clusters

Characteristics	Cluster A (n=25)	Cluster B (n=54)	Cluster C (n=6)
Females, n (%)	18 (72.0)	26 (48.1)	4 (66.7)
Age (y), mean ± SD	49.92±16.61	46.47±16.40	39.25±3.326
Cephalosporins, n (%)			
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)	2 (33.3)
Cefixime	0	3 (5.6)	2 (33.3)
Cefepime	0	1 (1.9)	0
Type of reaction, n (%)			
Urticaria	17 (68.0)	28 (51.9)	0
Anaphylaxis	8 (32.0)	26 (48.1)	6 (100.0)
Time since reaction to study (m) mean ± SD	26.64±46.28	7.37±19.29	65.67±144.45
Atopy, n (%)	4 (16.0)	6 (11.1)	1 (16.7)
Positive STs with penicillin determinants, n (%)			
Positive STs with AX, n (%)	3 (12.0)	2 (3.7)	4 (66.7)
Positive STs with the culprit cephalosporin, n (%)			
Positive STs with other cephalosporins, n (%)	1 (4.0)	9 (16.7)	5 (83.3)

AX: amoxicillin; STs: Skin tests.