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Cephalosporin and penicillin cross-reactivity in patients allergic to penicillins

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Key words

allergy – cephalosporins
– cross-reactivity – IgE –
penicillins – radio-
allergosorbent test

Abstract. Background: Beta-lactam antibiotics are the most commonly used antibiotics which usually cause serious IgE-mediated allergic reactions. Of all beta-lactam antibiotics, penicillins have so far been the best-studied, but the studies of cephalosporins and their cross-reactivity with penicillins are rare. We sought to evaluate the IgE response in vitro and estimate cross-reactivity between penicillins and cephalosporins in patients allergic to penicillins. **Methods:** We studied 87 control subjects and 420 subjects allergic to penicillins. Radioallergosorbent test (RAST) was performed to detect eight types of specific-penicillin IgE and eleven types of specific-cephalosporin IgE. The cross-reactivity and different molecules recognition by IgE were studied with a radioallergosorbent inhibition test. **Results:** Of 420 patients allergic to penicillins, 95 patients (22.62%) showed specific-cephalosporin IgE positive, 73 patients (17.38%) showed IgEs positive to both penicillins and cephalosporins. In specific-penicillin IgE positive group, the positive rate of specific-cephalosporin IgE was significantly higher than in specific-penicillin IgE negative group (27.14% vs. 14.57%, $p < 0.01$). In urticaria group, the positive rate of specific-cephalosporin IgE was significantly higher than in other symptoms group (30.65% vs. 8.11%, $p < 0.05$). The analysis of drugs which have the same or similar side-chains showed that benzylpenicillanyl-IgE (BPA-IgE), ampicillanyl-IgE (APA-IgE), amoxicillanyl-IgE (AXA-IgE) were respectively related to cephalothanyl-IgE (CLA-IgE), cephalaxanyl-IgE (CEXA-IgE), cephaloxanyl-IgE (CEXA-IgE) in sera of penicillin-allergic patients we studied, and compared with patients who had negative amoxicillin-IgE, the positive rates of specific-ampicillin IgE and specific-cephalexin IgE were significantly higher in patients who had positive amoxicillin-IgE (14.43% vs. 3.72%, 14.00% vs. 2.96%, $p < 0.01$). Radioallergosorbent test and radioallergosorbent inhibition test confirmed that both nuclear structure and R1 side-chain contribute to IgE recognition. **Conclusions:** There exists cross-reactivity between cephalosporins and penicillins;

patients allergic to several penicillins are more likely to develop allergic reaction to cephalosporins; due to sensitization to the similar structural characteristics (nuclear and R1 side-chain), penicillin-allergic patients may develop cross-allergic reactions with not only first-generation but also third-generation cephalosporins.

Introduction

Besides penicillins, cephalosporins represent the most commonly prescribed beta-lactams for treating common infections, [1, 2] such as bronchitis, otitis media, pneumonia, and cellulites. They are also administered as first-line prophylaxis for many types of surgical procedures. But meanwhile, they are easy to induce IgE-mediated reactions, [3, 4] which are manifested clinically by urticaria, rhinitis, bronchospasm, angioedema and anaphylactic shock [3, 4, 7].

The estimated risk of patients developing allergic reactions to cephalosporins range from 1% to 3% and is even higher in patients with a documented penicillin allergy. Early reports from the 1960s suggested that in patients with documented IgE-mediated hypersensitivity to penicillin, the rate of reaction to cephalosporins was as high as 30%, but in the 1980s, with the development of cephalosporins synthesis' technology, the rate of cephalosporins hypersensitivity reduced to about 10%. However, data of recent review available suggested that the positive rate seemed to be growing with the increasing administration of cephalosporins in clinical anti-bacteria therapy [8, 9, 10, 11, 12, 13, 53]. And approximately 1% to 8% of patients with positive specific-penicillin IgE are thought to develop an immediate-type hypersensitivity to cephalosporins [15, 41]. Numerous instances of docu-

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mented anaphylactic reactions, including fatalities, have happened in historically penicillin-allergic patients who have received cephalosporins [15, 16, 17, 18, 19, 20]. Since cephalosporins and penicillins share common β -lactam ring and same or similar side-chain, such as the side-chains of cefamandole, cefaloram, cephalothin, and cephaloridine are similar to penicillin G, the side-chain of cephalexin is similar to ampicillin and amoxicillin, this may be explained by their existing cross-reactivity between these two kinds of antibiotics [9, 11, 22, 24, 25].

The cross-reactivity between cephalosporins and penicillins has been examined in laboratory and clinical settings; nevertheless, this complex issue has not been resolved for the lack of serological research [8, 26]. The number of potential haptens is large, both side-chain and nuclear components, even the whole molecule structure of cephalosporins may participate in allergic reaction [8]. The variety of specific haptens involved in hypersensitivity to cephalosporins and the inadequate understanding of exactly what determinants' structures are involved, have delayed the development of test procedures for diagnosing cephalosporins hypersensitivity [28, 29, 30, 31, 32].

We conducted this prospective study to get information of cephalosporins allergy and to evaluate cross-reactivity between cephalosporins and penicillins in a group of subjects who had positive skin test or had allergic history to penicillins. In vitro, RAST assays were performed with 8 kinds of penicillin determinants and 11 kinds of cephalosporin determinants to assess corresponding specific IgE in sera; And a RAST inhibition assay was applied to assess the cross-reactivity.

Materials and methods

Subjects and grouping

The study included a total of 420 subjects (176 females, 244 males, age ranging from 18 to 22 years) and 87 control subjects (52 females, 35 males, age ranging from 18 to 60 years). All subjects were mainly recruited from First Affiliated Hospital of Zhengzhou University. The clinical characteristics of patients are summarized in Table 1.

Patient selection was based on a positive skin test or clinically allergic symptoms after penicillins' therapy. We obtain information about their illnesses, the time, allergic drugs, nature of previous apparently allergic reactions, allergic diseases and allergic family history according to patients' descriptions in detailed questionnaire that was designed by our team [49, 50, 51, 52].

Of the 420 penicillin-allergic patients who were enrolled in the study, 294 were recruited based on a positive skin test; the remaining 126 patients presented negative skin test but typically allergic symptoms after penicillins administration. These 126 patients were subdivided into three symptom groups: shock group, urticaria group, and other symptoms (pruritus, dyspnea, angioedema, bronchospasm, and other allergic symptoms except for shock and urticaria) group. Patients with allergic symptoms were also categorized as immediate group and delayed group according to the initial time of allergy. The immediate group was defined as presenting allergic symptoms within 1 h after drug administration, and the delayed group was defined as presenting allergic symptoms at > 1 h after drug administration. In order to investigate the relationship between specific-penicillin IgE and specific-cephalosporin IgE, we assayed specific-penicillin IgE using the radioallergosorbent test (RAST) and divided patients into a positive IgE group and a negative IgE group to evaluate the level of specific-cephalosporin IgE.

A total of 87 controls were recruited to set up the positive criterion of RAST (Table 1). These controls tested negative for the skin test and had administrated penicillins previously without any reported reaction. They also showed no allergic reaction (including drug, food, pollen, etc) and allergic disease (atopic dermatitis, allergic rhinitis, etc).

Before the study, all subjects received information about drawn blood, and signed written informed consent. The protocol was carried out with the approval of the Ethics Committee.

Blood samples

Blood samples were drawn from each subject and clotted for 2 h at room tempera-

Table 1. Clinical characteristics and part results of the specific IgE test of 87 controls and 420 patients allergic to penicillin.

Groups	Controls	Patients	Patients with positive specific-cephalosporin IgE (%)
All patients (n)	87	420	
Age (mean $\pm$ SD, range)	19.22 $\pm$ 1.45 (18 ~ 60)	19.09 $\pm$ 1.33 (18 ~ 22)	
Gender			
Male	35	244	54 (22.13)
Female	52	176	41 (23.30)
Skin test ^a			
Positive skin test		294	66 (22.45)
Negative skin test		126	29 (23.02)
Allergic symptoms ^b			
Shock		27	7 (25.93)
Urticaria		62	19 (30.65)*
Other symptoms		37	3 (8.11)
Allergic type ^c			
Immediate reactions		68	17 (25.00)
Delayed reactions		58	12 (20.69)
Specific-penicillin IgE level ^d			
IgE Positive		269	73 (27.14)**
IgE Negative		151	22 (14.57)

^aOf the 420 penicillin allergic patients, 294 were recruited based on a positive skin test; the remaining 126 patients presented negative skin test but typical allergic symptoms after penicillin administration. ^bA total of 126 patients presented penicillin allergic symptoms. Other patients just presented positive skin test but no systemic symptom. ^cPatients with penicillin allergic symptoms were categorized as immediate group (1 h) and delayed group (> 1 h) according to the initial time of allergic symptoms. ^dAccording to specific-penicillin IgE level, patients are divided into IgE positive group (either one kind of eight specific-penicillin IgE values over the mean + 2.33 standard deviation of control) and IgE negative group (all eight kinds of specific-penicillin IgE values below the mean + 2.33 Standard deviation of control). * $p < 0.05$, vs. other symptoms, ** $p < 0.01$, vs. IgE negative.

ture. After that, the sera were separated and stored at -20°C until the in vitro tests were performed.

Skin test

The Penicillin G sodium salt was diluted in saline solution to 200 U/ml. Approximately 0.1 ml (20 U) was injected for intradermal testing on the inner side of the forearm, the diameter of wheal was measured

after 20 minutes and the reaction was considered positive when the diameter was greater than 5 mm with a surrounding area of erythema.

Specific IgE by radioallergosorbent (RAST)

The vitro specific IgE detection was made by radioallergosorbent (RAST), using several major and minor determinant paper discs that displayed in Table 2.

The paper discs of major and minor antigenic determinant were prepared following a modification of the method by Zhao et al. [48] And RAST assay are performed as previously described [26, 33].

The RAST results reflected the radio-labeled substance uptake, expressed as a percentage of the maximum counts per minute (cpm) added. Values over the mean + 2.33 standard deviation (SD) of the results in the control group for BPO, PVO, APO, AXO, CEXO, CLO, CEZO, CPZO, CTO, CZO, CXO, BPA, PVA, APA, AXA, CEXA, CLA, CEZA, and CPZA were considered to be positive. (All the “cephalosporoyl” and “cephalosporanyl” we inferred are series of heterogeneous degradation fragments after the cephalosporoyl and cephalosporanyl formation)

RAST inhibition assay

In vitro determination of cross-reactivity was performed by RAST inhibition assay. Sera which had values (RAST) higher than 4% were incubated with 11 different kinds of betalactams (PG, PV, AP, AX, CEX, CL, CEZ, CPZ, CT, CZ, CX), 2 different kinds of nuclear structures (6-APA, 7-ACA), as well as 4 different kinds of side-chain structures (PHA, PHOA, NPG, PHPG) in three 10-fold decreasing concentrations (100 mMol/l, 10 mMol/l and 1 mMol/l) for 3 h, then the corresponding betalactam-PLL disc was added. Next, several procedures were followed as the continued RAST procedure was described above. The results were expressed as percentage inhibition with respect to the non-inhibited serum. Comparison of the inhibition

Table 2. The antibiotics and corresponding major or minor determinant paper discs are involved in the study.

Antibiotics (abbreviation)	Major determinant paper discs (Abbreviation)	Minor determinant paper discs (abbreviation)
Penicillins		
Benzylpenicillin (PG)	benzylpenicilloyl-polylysine (BPO-PLL)	benzylpenicillanyl-polylysine (BPA-PLL)
Phenoxymethylpenicillin (PV)	phenoxymethylpenicilloyl-polylysine (PVO-PLL)	phenoxymethylpenicillanyl-polylysine (PVA-PLL)
Ampicillin (AP)	ampicilloyl-polylysine (APO-PLL)	ampicillanyl-polylysine (APA-PLL)
Amoxicillin (AX)	amoxicilloyl-polylysine (AXO-PLL)	amoxicillanyl-polylysine (AXA-PLL)
Cephalosporins		
Cephalexin (CEX)	cephalexoyl-polylysine (CEXO-PLL)	cephalexanyl-polylysine (CEXA-PLL)
Cephalothin (CL)	cephalothoyl-polylysine (CLO-PLL)	cephalothanyl-polylysine (CLA-PLL)
Cefazolin (CEZ)	cefazoyl-polylysine (CEZO-PLL)	cefazolanyl-polylysine (CEZA-PLL)
Cefoperazone (CPZ)	cefoperazoyl-polylysine (CPZO-PLL)	cefoperazanyl-polylysine (CPZA-PLL)
Ceftriaxone (CT)	ceftriaxoyl-polylysine (CTO-PLL)	–
Ceftazidime (CZ)	ceftazidoyl-polylysine (CZO-PLL)	–
Cefotaxime (CX)	cefotaxoyl-polylysine (CXO-PLL)	–

– means this article did not involve synthetic technology.

capacity of the monomeric conjugates was made at 50% inhibition.

Statistical Analysis

Categorical data were given as numbers of cases and percentages, and they were compared by using a χ^2 -test. A p value of 0.05 or less indicated statistical significance.

Results

The positive rate of specific IgE

We evaluated 8 kinds of specific-penicillin IgE and 11 kinds of specific-cephalosporin IgE in sera of 87 controls and 420 allergic patients by RAST. Of 87 controls, the specific IgEs were all below the positive standard. Of 420 allergic patients, the positive rate of specific-penicillin IgE was 64.05% (269), while the positive rate of specific-cephalosporin IgE was 22.62% (95).

Of 294 skin test positive subjects, 22.45% (66) showed RAST-positive to cephalosporins, while of 126 subjects with negative skin

test but positive allergic symptoms, 23.02% (29) showed specific-cephalosporin IgE positive (Table 1). According to different allergic symptoms of these 126 patients, the positive rate of specific-cephalosporin IgE in urticaria group was higher than that in other symptoms group ($p < 0.05$) (Table 3).

It was evident that RAST-positive rate to cephalosporins had increased significantly from examining 1 – 4 kinds (7.38%, 10.95%, 14.05%, 16.19%, respectively) to examining 11 kinds (22.62%) by increasing the number of tested antigenic determinants ($p < 0.05$).

Among the 11 kinds of specific-cephalosporin IgE (CEXO-IgE, CLO-IgE, CEZO-IgE, CPZO-IgE, CXO-IgE, CTO-IgE, CEO-IgE and CEXA-IgE, CLA-IgE, CEZA-IgE, CPZA-IgE) we examined, the positive rate of CPZA-IgE was highest (7.38%) and CTO-IgE was the lowest (2.62%) (Table 4).

Cross-reactivity between penicillins and cephalosporins

Among 420 penicillin allergic patients, 73 patients (17.38%) showed IgE level's cross-

Table 3. The positive rate of specific-cephalosporin IgE in patients with different penicillin allergic symptoms.

Group	Case (n)	Case with positive specific-cephalosporin IgE (n)	IgE positive rate (%)
Anaphylactic shock	27	7	25.93
Urticaria	62	19	30.65*
Other symptoms	37	3	8.11
Total	126	29	23.02

* $p < 0.05$, vs. other symptoms.

Table 4. The positive rate of different specific-cephalosporin IgE in patients allergic to penicillin (n = 420).

Antibiotics	Antibodies	Case with positive specific-cephalosporin IgE (n)	IgE positive rate (%)
Cephalexin	CEXO	20	4.76
	CEXA	14	3.33
Cephalothin	CLO	24	5.71
	CLA	24	5.71
Cefazolin	CEZO	17	4.05
	CEZA	23	5.48
Cefoperazone	CPZO	12	2.86
	CPZA	31	7.38
Ceftriaxone	CTO	11	2.62
Ceftazidime	CZO	28	6.67
Cefotaxime	CXO	23	5.48
Total	Total	95	22.62

CEXO = cephalexoyl; CLO = cephalothoyl; CEZO = cefazoloyl; CPZO = cefoperazoyl; CTO = ceftriaxoyl; CZO = ceftazidoyl; CXO = cefotaxoyl; CEXA = cephaloxanyl; CLA = cephalothanyl; CEZA = cefazolanyl; CPZA = cefoperazanyl.

reactivity between penicillins and cephalosporins. Among 269 patients with positive specific-penicillin IgE, APA-IgE had the highest cross-reactivity rate with CLA-IgE and CPZA-IgE which was up to 25.64%, and BPO-IgE had the lowest cross-reactivity rate with CTO-IgE, which was only 2.46% (Table 5). With positive kinds of specific-penicillin IgE increasing, a statistically higher rate of positive results on IgE assays for cephalosporins was among patients who had 4 – 8 kinds of specific-penicillin IgE positive, as compared with those patients who had none or only one kind positive ($p < 0.01$) (Table 6). The positive level and rate of specific-cephalosporin IgE differences between spe-

cific-penicillin IgE positive and negative group were showed in Table 7 and Table 8.

The analysis of drugs which have the same or similar side-chains showed that benzylpenicillanyl-IgE (BPA-IgE), ampicillanyl-IgE (APA-IgE), and amoxicillanyl-IgE (AXA-IgE) were respectively related to cephalothanyl-IgE (CLA-IgE), cephaloxanyl-IgE (CEXA-IgE), cephaloxanyl-IgE (CEXA-IgE) in sera of penicillin-allergic patients we studied, and compared with patients who had negative amoxicillin-IgE, the positive rates of specific-ampicillin IgE and specific-cephalexin IgE were significantly higher in patients who had positive amoxicillin-IgE (14.43% vs. 3.72%, 14.00% vs. 2.96%, $p < 0.01$). But there was no significant difference in positive rate of specific-cephalothin IgE between specific-penicillin G IgE positive and negative group ($p > 0.05$).

RAST inhibition assays

To study specificity and cross-reactivity in more detail, we selected 2 typical cases to carry on RAST inhibition assays. Case 3 was allergic to both penicillins and cephalosporins, case H11 was only allergic to penicillin G. These two patients' allergic information was displayed in Table 9, and the results of RAST inhibition assays are shown in Figures 1 – 4.

From Figure 1 and 2 we can conclude that the side-chain which owned more than 75% of inhibition values seemed to be the key point in cross-reactivity in Case 3. As for case H11, the inhibition rates of 6-APA and 7-ACA were about 70% at 100 mmol/l and indicated that the antibodies in this patient seemed to recognize nuclear structures.

Discussion

Although allergic reactions to cephalosporins was rare before the 1990s [34], with the increasing use of cephalosporins in clinically antibacterial therapy, the number of subjects primarily sensitized to cephalosporins is increasing, too [35, 36].

Some investigations informed that the chance of allergies to cephalosporins in patients hypersensitive to penicillins was eight

Table 5. The positive rate of cross-reactivity between different specific IgE in 269 allergic patients with positive penicillin IgE(%).

Group	Cases (n)	CEXO	CLO	CEZO	CPZO	CTO	CZO	CXO	CEXA	CLA	CEZA	CPZA
BPO	122	6.56	5.74	5.74	2.46	2.46	9.02	4.10	4.10	6.56	4.92	8.20
PVO	116	8.62	6.90	8.62	4.31	5.17	9.48	6.90	2.59	12.07	9.48	13.79
APO	73	8.22	9.59	9.59	4.11	4.11	16.44	10.96	4.11	13.70	6.85	12.33
AXO	119	10.08	9.24	5.04	3.36	4.20	9.24	8.40	5.04	11.76	8.40	9.24
BPA	60	10.00	11.67	11.67	3.33	8.33	13.33	11.67	3.33	16.67	15.00	20.00
PVA	51	3.92	11.76	5.88	5.88	7.84	15.69	9.80	3.92	15.69	13.73	19.61
APA	39	15.38	10.26	15.28	2.56	2.56	15.38	7.69	5.13	25.64	2.56	25.64
AXA	48	20.83	16.67	14.58	4.17	10.42	20.83	14.58	4.17	18.75	18.75	25.00

BPO = benzylpenicilloyl; PVO = phenoxymethylpenicilloyl; APC = ampicilloyl; AXO = amoxicilloyl; BPA = benzylpenicillanyl; PVA = phenoxymethylpenicillanyl; APA = ampicillanyl; AXA = amoxicillanyl; CEXO = cephaloxoyl; CLO = cephalothoyl; CEZO = cefazoloyl; CPZO = cefoperazoyl, CTO = ceftriaxoyl; CZO = ceftazidoyl; CXO = cefotaxoyl; CEXA = cephalexanyl; CLA = cephalothanyl; CEZA = cefazolanyl; CPZA = cefoperazanyl.

Table 6. The positive rate of specific-cephalosporin IgE in different Penicillin-allergic group.

Group	Cases (n)	Cases with positive specific-cephalosporin IgE	Positive rate of specific-cephalosporin IgE (%)
0 antibody positive	151	22	14.57*
1 antibody positive	108	19	17.59*
2 antibodies positive	60	14	23.33
3 antibodies positive	46	11	23.91
4 antibodies positive	31	14	45.16
5 antibodies positive	14	8	57.14
6 antibodies positive	6	3	50
7 antibodies positive	2	2	100
8 antibodies positive	2	1	50

*p < 0.01, vs. 4 – 8 antibodies positive group.

times higher than that in patients who are not. Administering cephalosporins to penicillin-allergic patients who might benefit from cephalosporins treatment is often deferred for the fear of cross-reactivity [4]. For these patients, prophylactic skin tests with cephalosporins are not routinely performed, [37, 38, 39, 40, 41, 42] although some allergists perform skin tests for both penicillins and cephalosporins in question before giving cephalosporins to patients [43, 44]. This can be explained by the following reasons: First, the degradation products of cephalosporin are not available for testing skin at the present stage, so when we perform skin test with the native molecule, false negative case may come up. Second, since the available cephalosporin skin tests are lack of standard operat-

ing procedure (SOP), there is the potential for false-positive tests from non-specific irritant reactions in non-allergic patients [6, 21, 41]. However, some studies took patients with immediate allergic-reactions to cephalosporins as investigated subjects, and examined the IgE responses by performing RASTs. The IgE responses showed good correlation with the culprit cephalosporins [23]. But so far, in penicillin-allergic patients, the general information concerning the response to different penicillins and cephalosporins has been lacking [5, 11, 45]. In our study, we combined skin tests and RAST together to examine 11 kinds of specific-cephalosporin IgE in 87 controls and 420 penicillin-allergic patients. The RAST result consisted with clinical data: all controls' IgEs under the positive standards while 22.62% patients showed specific-cephalosporin IgE positive. Regardless of patients with positive skin test or with allergic symptom, the positive rate of specific-cephalosporin IgE had no significant differences, but for different allergic symptoms, the positive rate of patients with urticaria was statistically higher than patients with other symptoms. This indicated that if a patient developed urticaria to penicillins, he would be more likely to be allergic to cephalosporins than to developed other symptoms. As we know, major determinants are related to immediate hypersensitivity while minor determinants are contrarily related to delayed hypersensitivity. We examined 11 kinds of specific-cephalosporin IgE, and found that the positive rate of cefoperazone minor determinant corresponding IgE (CPZA-IgE) was highest and the positive

Table 7. The IgE levels of specific-cephalosporin in patients with positive and negative specific-penicillin IgE(%) ($\bar{x} \pm s$).

Antibiotics	Antibodies	Specific-penicillin IgE positive (n = 269)	Specific-penicillin IgE negative (n = 151)	t	p
Cephalexin	CEXO	0.70 $\pm$ 0.45	0.64 $\pm$ 0.33	1.520	> 0.05
	CEXA	0.77 $\pm$ 2.09	0.64 $\pm$ 0.20	0.752	> 0.05
Cephalothin	CLO	1.19 $\pm$ 0.68	0.97 $\pm$ 0.46	3.797	< 0.01
	CLA	0.61 $\pm$ 0.42	0.57 $\pm$ 0.50	1.002	> 0.05
Cefazolin	CEZO	1.19 $\pm$ 0.67	1.11 $\pm$ 0.61	1.249	> 0.05
	CEZA	0.80 $\pm$ 0.74	0.62 $\pm$ 0.31	3.567	< 0.01
Cefoperazone	CPZO	0.64 $\pm$ 0.41	0.58 $\pm$ 0.40	1.318	> 0.05
	CPZA	0.81 $\pm$ 0.66	0.63 $\pm$ 0.40	3.381	< 0.01
Ceftriaxone	CTO	0.85 $\pm$ 0.64	0.73 $\pm$ 0.41	2.118	< 0.05
Ceftazidime	CZO	0.74 $\pm$ 0.64	0.68 $\pm$ 0.85	0.826	> 0.05
Cefotaxime	CXO	0.83 $\pm$ 0.55	0.83 $\pm$ 0.52	0.003	> 0.05

CEXO = cephalexoyl; CLO = cephalothoyl; CEZO = cefazoloyl; CPZO = cefoperazoyl, CTO = ceftriaxoyl; CZO = ceftazidoyl; CXO = cefotaxoyl; CEXA = cephalaxanyl; CLA = cephalothanyl; CEZA = cefazolanyl; CPZA = cefoperazanyl.

Table 8. The positive rate of specific-cephalosporin IgE in patients with positive and negative specific-penicillin IgE(%).

Antibiotics	Antibodies	Penicillin IgE positive	Penicillin IgE negative
Cephalexin	CEXO	6.69*	1.32
	CEXA	3.72	2.65
Cephalothin	CLO	7.43*	2.65
	CLA	7.81*	1.99
Cefazolin	CEZO	5.20	1.99
	CEZA	7.81*	1.32
Cefoperazone	CPZO	2.97	2.65
	CPZA	10.04*	2.65
Ceftriaxone	CTO	3.72	0.66
Ceftazidime	CZO	8.92*	2.65
Cefotaxime	CXO	6.32	3.31

*p < 0.01, vs. Penicillin IgE Negative; CEXO = cephalexoyl; CLO = cephalothoyl; CEZO = cefazoloyl; CPZO = cefoperazoyl, CTO = ceftriaxoyl; CZO = ceftazidoyl; CXO = cefotaxoyl; CEXA = cephalaxanyl; CLA = cephalothanyl; CEZA = cefazolanyl; CPZA = cefoperazanyl.

Table 9. Clinical characteristics of patients included in the study.

No.	Age	Gender	Drugs	Allergic response	Skin test	Positive specific IgE
3	20	M	PG Cephalosporin	urticaria	–	AXA, CEXA
H11	19	M	PG	urticaria	+	BPO, APA, CZO

+ means skin test positive, – means skin test negative.

rate of ceftriaxone major determinant corresponding IgE (CTO-IgE) was the lowest. That is to say, cefoperazone is more likely to bring about delayed hypersensitivity but immediate hypersensitivity induced by ceftriaxone is rare.

From the viewpoint of specific-penicillin IgE positive or not, the following conclusions can be made in our research: First, no matter positive rates or positive levels of CEZA-IgE and CPZA-IgE, patients with positive specific-penicillin IgE were significantly higher than patients with negative specific-penicillin IgE, so patients with positive specific-penicillin IgE seem more likely to develop cefazolin and cefoperazone allergy. Second, in patients who had 4–8 kinds of specific-penicillin IgE positive, the positive rate of specific-cephalosporin IgE was higher than patients who had none or only one kind specific-penicillin IgE positive, so the more kinds of penicillins one patient is allergic to, the more likely he would be allergic to cephalosporins. So if a patient was allergic to several penicillins, for safety's sake, it would better to not administrate cephalosporins. However, the question of whether some patients developed a response to cephalosporins because of cross-reactivity with penicillins or because of coexisting sensitivity is difficult to answer.

The cross-reactivity among cephalosporins and between cephalosporins and penicil-

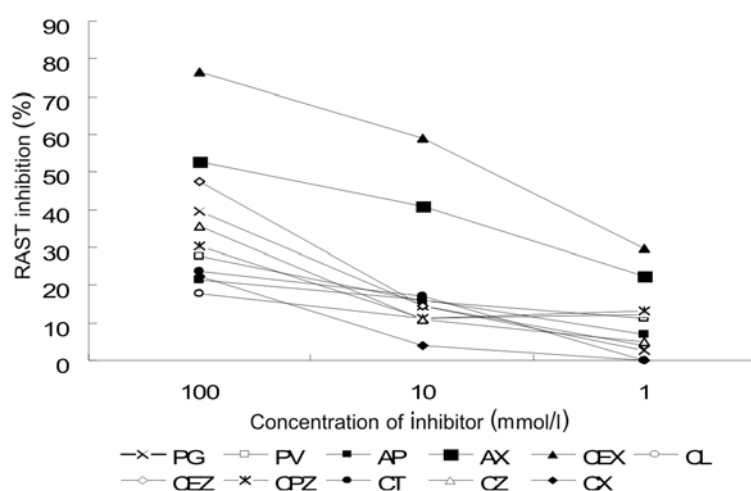


Figure 1. RAST inhibition patterns obtained with serum 3, different penicillins and cephalosporins as inhibitors.

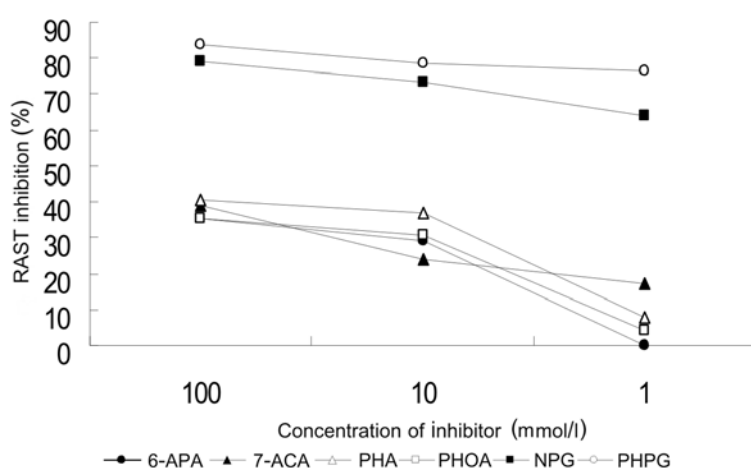


Figure 2. RAST inhibition patterns obtained with serum 3, different chemical structures representing parts of penicillins and cephalosporins as inhibitors.

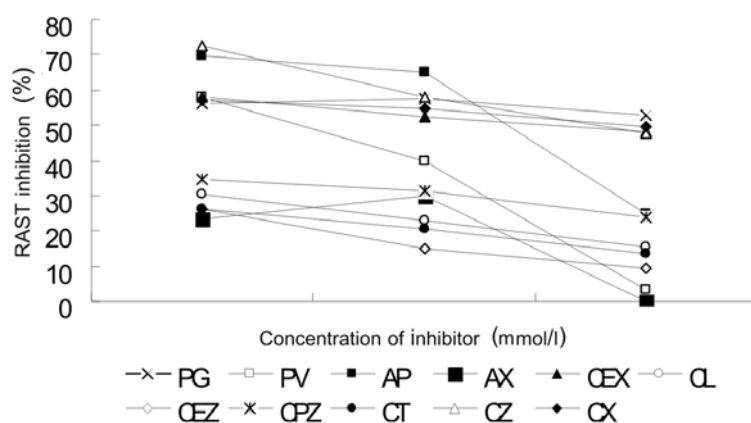


Figure 3. RAST inhibition patterns obtained with serum H11, different penicillins and cephalosporins as inhibitors.

lins has been examined in laboratory and clinical settings [8, 26]. And in our study, 73 patients (17.38%) showed IgE level's cross-sensitivity between penicillins and cephalosporins. The ratio is consistent with former studies 10–30% [8, 9, 10, 11, 12, 13, 53]. Individual penicillins and cephalosporins are distinguished by a side-chain (R1) attached to the beta-lactam ring through an amide linkage, whereas for cephalosporins, the R2 substituent at the 3-position on the dihydrothiazine ring provides an additional distinguishing point for individual members of the family (Figure 5). The early studies showed moderate cross-reactivity between cephalosporins and penicillins because they share a common β -lactam ring, [27, 34] but later investigators found that most of the cross-reactivity between penicillins and cephalosporins had involved first- and second-generation cephalosporins because of side-chain structural similarities; [11, 21] however, the cross-reactivity between penicillins and second- or third-generation cephalosporins (excluding cefamandole) was rare [14]. This finding attracted researchers' attention. They began to focus on the character of side-chain and proved that the side-chain plays an important role in cross-reactivity. With time researcher realized that the number of potential haptens was large, both side-chain and nuclear components, even the whole drug molecule or a small side-chain group (methyl) of cephalosporins may participate in the hypersensitivity reaction [8, 27]. In our study, there is a large degree of consensus between the minor determinants IgE levels of penicillins (penicillin G, amoxicillin and ampicillin) and first-generation cephalosporins (cefalexin and cephalothin) which have the same or similar side-chain structures. However, the result also showed that APA-IgE had the highest cross-reactivity with CLA-IgE and CPZA-IgE which was up to 25.64%. This is to say, side-chain not only plays an important role in cross-reactivity between penicillins and first-generation cephalothin, but also plays a role in cross-hypersensitivity between penicillins and third-generation cefoperazone. To a certain extent, this is distinguished with Anne S, Reisman RE's research mentioned above. These novel findings may in part, be explained by the following reason: although the side-chain structure of first-generation cephalosporins are more similar to peni-

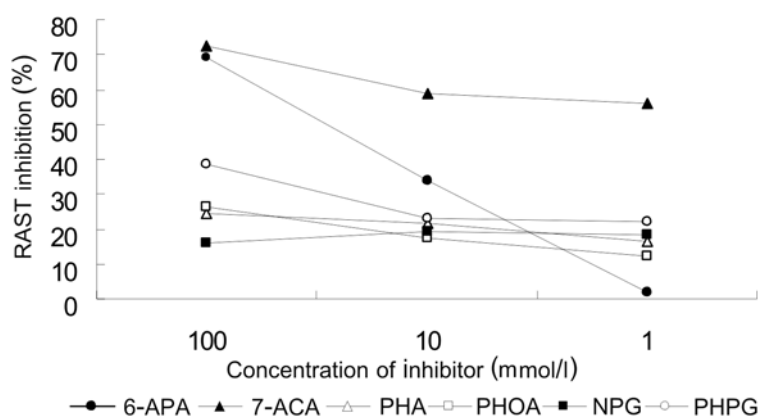


Figure 4. RAST inhibition patterns obtained with serum H11, different chemical structures representing parts of penicillins and cephalosporins as inhibitors.

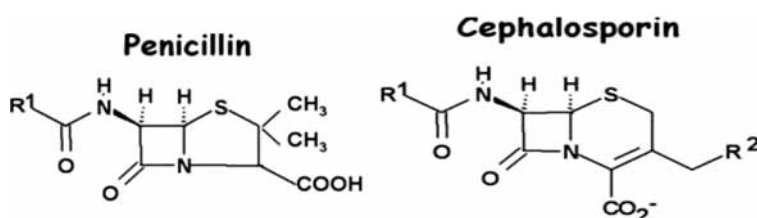


Figure 5. General structures of cephalosporins and penicillins.

cillins, so far the detailed recognition process of IgEs have not been so clearly illustrated. In addition, to the individual variance of allergic populations and antibiotics' using habits, these research findings defined in a Chinese population may be different to the results from western countries. In order to observe concrete recognition structure, two patients' serums with typically high IgEs in RAST were performed by RAST inhibition assays. In one case, side-chain structures (NPG, PHPG) provided about an 80% inhibition rate while in another case, the nuclear structures (6-APA and 7-ACA) gave about a 70% inhibition rate. Different behavior of IgEs in recognizing antigenic sections tell us that both nuclear and side-chain structure of beta-lactam antibiotics can cause cross-allergic reactions. Our research confirmed once again the diversity of IgEs in recognizing beta-lactam antibiotics. Therefore, beta-lactam antigens used for skin test and in-vitro assays for IgE should permit the detection of sensitivity to side-chain and nuclear structure of beta-lactams, moreover, test should include major determinants for "-oyl" and minor de-

terminants for "-anyl" specificity. A selected battery of determinants should be employed, for some individuals reacting to one or more beta-lactams but not others or to "-oyl" but not "-anyl" specificities (or vice versa).

Conclusion

To our knowledge, this is the first assay to examine cross-reactivity between penicillins and cephalosporins in so many penicillin-allergic patients by in-vivo skin test and in-vitro RAST. It is also the first assay to test so many cephalosporin determinants in so many penicillin-allergic patients by a penicillin way, though each determinant may be a series of compounds and we do not know the exact structure of them clearly. Because most reactions to cephalosporins are IgE-mediated, and our former research informed that the in-vitro test-RAST show good correlation with skin test result, penicillins and cephalosporins skin testing and RAST appear to be useful tools for evaluating such reactions, and the IgE assay for penicillins and cephalosporins could be used as a complementary test to assess cross-reactivity [46].

The main findings of our study are as follows: There exists cross-reactivity between cephalosporins and penicillins; patients allergic to several penicillins are more likely to develop cephalosporins allergic reaction due to sensitization to the similar structural characteristics (nuclear and R1 side-chain). Not only first-generation but also third-generation cephalosporins may develop cross-allergic reactions with penicillins in penicillin-allergic patients.

Further studies should be carried out to fully understand the exact chemical structures of cephalosporin haptenic determinants, genetic and environmental influences in the pathogenesis of hypersensitivity to this kind of antibiotics and establish the effectively diagnostic tests to protect patients from an allergic reaction [47, 49, 50, 51, 52].

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