

Immediate Cephalosporin Allergy

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ABSTRACT

Background

Patients who suffer from acute IgE-mediated allergy to a cephalosporin antibiotic are frequently assumed to be at high risk of allergy to other cephalosporins and penicillins.

Objective

To define cross-reactivity patterns in patients with confirmed allergy to a cephalosporin.

Methods

Subjects presenting with a history of immediate allergy to a cephalosporin-family antibiotic between March 2009 to July 2017 were investigated with specific IgE (sIgE) testing to penicillin, amoxicillin and cefaclor, followed by skin prick testing (SPT), intradermal testing (IDT) and drug provocation testing (DPT) with a panel of penicillins and cephalosporins.

Results

Out of 564 subjects with a reported beta-lactam allergy, 90 identified a cephalosporin as their index drug. Fifty five (61.1%) of the 90 subjects tested had a history consistent with an IgE mediated reaction, of whom 24 (43.6%) were proven to be allergic to their index cephalosporin. Twenty (83.3%) of the 24 were allergic only to their index cephalosporin. Of the four remaining subjects, two were co-sensitised to another beta-lactam with a similar side chain, while the other two had no specific cross-reactivity pattern. Major and minor penicillin determinants were negative for all cephalosporin-allergic individuals.

Conclusion

In our cohort, cephalosporin allergy does not appear to be a class effect, with most cases found allergic only to their index cephalosporin. Co-sensitisation to other cephalosporins or penicillins was uncommon, and when it occurred, was usually consistent with side chain cross-reactivity.

KEY WORDS

Cephalosporin allergy, IgE mediated, cross-reactivity, beta lactam, side chain

INTRODUCTION

Beta-lactams are the most commonly used first-line antibiotics globally, with cephalosporin use approaching penicillin use in recent decades.[1-3] It was previously reported that a cross-reactive cephalosporin allergy occurs in 10% of penicillin-allergic patients.[4] This figure relates to studies prior to the 1980s, which demonstrated cross-reactivity between benzylpenicillin and first and second generation cephalosporins. However, early cephalosporin products may have been contaminated by penicillin.[5] More recent studies have reported the rate of cephalosporin allergy in penicillin-allergic individuals to be 1-3%.[6-10] The rate of penicillin allergy in those primarily sensitised to cephalosporins is likely to be lower.[11]

Despite these recent findings, the recommendation to avoid all beta-lactams when suspected of a penicillin or cephalosporin allergy remains prevalent. While this might be justified on the basis of reduction of risk of adverse reactions, the exclusion of penicillins and cephalosporins has well-documented consequences including greater use of second-line agents[12] at greater cost[13, 14], with longer hospital stays and more readmissions.[15, 16] Therefore, more accurate antibiotic allergy labelling and a better understanding of cross-reactivity risks should reduce cost and improve safety.[17]

It has been shown that for penicillins, the core beta-lactam ring, the R side chain, or the entire penicillin molecule can act as the antigenic determinants, whereas for cephalosporins, the major site for immunogenic specificity appears to be the R1 side chain.[18, 19] This is independent of

cephalosporin generations, which refer to chronological development and antimicrobial spectrum but have little to do with structural similarities. This may narrow down the likelihood of cross-reactivity between penicillins and cephalosporins and re-frame the cross-reactivity risk assessment in terms of side chain similarity, both within the penicillin and cephalosporin families and between penicillins and cephalosporins with similar side chains.[20]

We sought to verify this in our own cohort by conducting a retrospective review of subjects with confirmed immediate cephalosporin allergy.

METHODS

Design overview

We conducted a retrospective review of the Royal Adelaide Hospital Immunology Procedure database focusing on the presentations, investigations and outcomes of subjects suspected of an immediate allergy to a cephalosporin. Ethics approval exemption was granted for this audit, as specified in the Central Adelaide Local Health Network Human Research Ethics Committee guidelines.

Subject selection

Using the database, we performed a search of subjects evaluated for beta-lactam allergy in the Immunology Day Unit between March 2009 and July 2017. We extracted subjects whose suspected allergy (index reaction) was to a cephalosporin. We reviewed their hospital records and included subjects whose history was consistent with an immediate allergic reaction. (*Figure 2*) This was defined as a reaction commencing within an hour of exposure to a cephalosporin and with typical

IgE mediated symptoms including urticaria, angioedema, bronchospasm, abdominal pain, vomiting, diarrhea, presyncope or hypotension.

Investigations consisted of a stepwise progression of *in vitro* specific IgE testing (sIgE), *in vivo* skin testing [skin prick testing (SPT), intradermal testing (IDT)] and/or drug provocation testing (DPT). A positive sIgE, SPT, IDT and/or DPT result to the suspected index cephalosporin would confirm the cephalosporin allergy and no further testing would proceed with that cephalosporin; however, skin testing or drug provocation testing to alternative beta-lactams may occur.

Detection of specific IgE in serum

Subjects were tested for specific IgE to penicilloyl V, penicilloyl G, amoxicilloyl, ampicilloyl and cefaclor using ImmunoCAP (Thermo Fisher Scientific Inc), with a cutoff of 0.35 kU/L.

Skin prick and intradermal testing

Standard skin testing was to Diater DAP Major Determinant Benzyl penicilloyl-polylysine (PPL), Diater DAP Minor Determinant Mix (MDM), benzylpenicillin, amoxicillin and cefazolin. Additional cephalosporins tested were based upon the allergy history. Cephalosporins available only in oral capsule form (e.g. cephalexin and cefaclor) were prepared in solution for skin testing by the Royal Adelaide Hospital pharmacy, by dissolving the contents of the capsule in water to a dilution of 3mg/ml followed by 0.2 micron filtration. Subjects underwent a 3 step IDT progression of concentrations (*Table 1a*) with an observation period of 20 minutes between each step.

Drug provocation testing

A 3 step oral or intravenous drug provocation test (*Table 1b*) was employed with an hour between each dose increase and two hours of observation after the final dose. The patient would be

challenged with the index drug by default unless sIgE or skin testing were positive, in which case an alternative beta-lactam would be chosen for challenge.

RESULTS

Out of 564 subjects investigated for a beta-lactam allergy, 90 had a cephalosporin as their index drug. Fifty-five (61.1%) of the 90 subjects had a history consistent with an IgE mediated allergic reaction to a cephalosporin while the remaining 35 had a history of delayed type reaction or a less defined history. (*Figure 2*) Forty-six (51.1%) out of 90 subjects with a history of allergy to a cephalosporin were negative for sIgE, SPT, IDT and DPT to their index cephalosporin and were therefore delabelled of their cephalosporin allergy.

There were no adverse events during SPT or IDT and only 1 (1%) subject was reported to have experienced transient hypotension on DPT, which resolved spontaneously. Rescue adrenaline was not needed in any of the 90 subjects tested.

The mean of age of the 55 subjects with a history of immediate cephalosporin allergy was 49.9 with ages ranging from 20 to 84 years. Thirty two (58.1%) of the 55 had their index reaction within 5 years of testing while 11 (20%) had their reactions greater than 5 years previously, with no documentation of actual time point of reaction in the remainder. Erythema, urticaria and angioedema were the most prevalent symptoms, with 9 (16.3%) subjects describing severe symptoms with hypotension (anaphylaxis). (*Table 2*) Cephalexin was the most common index cephalosporin at 25 (45.4%) followed by cefazolin, 11 (20%) and ceftriaxone, 7 subjects (12.7%).

Twenty-four of the 55 subjects (43.6%) were proven to be allergic to their index cephalosporin. (*Table 3*) In 16 (66%) cases, confirmation was through sIgE and skin testing. All cefaclor-allergic

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subjects were diagnosed via sIgE. Since no sIgE testing is available, cefazolin and ceftriaxone allergy were diagnosed through intradermal testing in 83.3% and 75% of cases, the remainder were diagnosed with challenge. In contrast, 77.7% of cephalixin allergic subjects were confirmed through a positive DPT in the context of negative cephalixin skin testing. (*Figure 3*) Cefazolin intradermal testing was negative in all patients with challenge-proven allergy to cephalixin and ceftriaxone. Nine (16.3%) out of the 55 subjects were not tested to their index drug either due to a strong clinical history of anaphylaxis or clinical indication requiring testing to a specific alternative antibiotic. Twenty (83.3%) of the 24 cephalosporin allergic subjects were found allergic only to their index cephalosporin. One cephalixin-allergic subject had positive testing (sIgE and SPT) to amoxicillin which was in the context of a previous immediate allergic reaction to amoxicillin. Another cephalixin-allergic subject who had a positive sIgE to both amoxicillin and cefaclor later underwent DPT to amoxicillin which was also positive; thereby confirming an allergy to both amoxicillin and cephalixin. (*Table 4*)

One ceftriaxone allergic subject had a positive IDT to cephalixin. This subject went on to a DPT to amoxicillin which was negative. It is possible that this subject has co-sensitisation to both cephalosporins, although there was no previous history of a reaction to cephalixin. The patient did not undergo challenge with cephalixin and the positive predictive value of cephalixin IDT is not known, although 2 of 9 (22.2%) cephalixin allergic subjects in our group were diagnosed through positive IDT. A cefazolin allergic subject, confirmed on DPT, was also found allergic to cephalixin on DPT. This subject was negative to cefaclor on sIgE and to all penicillin determinants on skin testing.

Two cefaclor-allergic subjects confirmed by positive sIgE were also positive to other penicillins on sIgE (penicilloyl V in one and penicilloyl V, penicilloyl G and amoxicilloyl, in the other). Following

negative intradermal testing, both underwent DPT to amoxicillin which they tolerated. Importantly, major and minor penicillin antigenic determinants were negative by IDT for all cephalosporin-allergic subjects. (Table 4)

Skin test positivity for those with suspected immediate cephalosporin allergies is reported to wane over time.[21] In our cohort, the majority of subjects had their reaction occur within 5 years of their testing. Of the 55 subjects with a history consistent of an immediate allergy, 7 subjects who had their index reaction greater than five years previously were tested to their index cephalosporin, 4 of whom demonstrated negative skin tests. All but one of the 4 subjects tolerated a DPT to their index cephalosporin. Another subject with a history of a cephalothin reaction 9 years previously had a positive IDT to cephalothin.

DISCUSSION

A recent study considering antimicrobial drug allergies in a tertiary referral centre demonstrated a 5% prevalence of reported cephalosporin allergy, compared to 10% for penicillin.[22] In our cohort, comprising referrals from both in-patient and out-patient settings, the number of subjects tested for cephalosporin allergy was around a fifth that of those tested for penicillin allergy (90 cephalosporin vs 474 penicillin).

Currently, the only commercially available *in vitro* test for cephalosporins in Australia is cefaclor, with a reported sensitivity of 80.2% and specificity of 81.6% at 0.11 kU/L cut-off.[23] In our cohort, 4 out of the 5 suspected cefaclor allergic subjects were sIgE positive to cefaclor at a cut-off of 0.35 kU/L. A positive sIgE to cefaclor in the presence of a consistent history was taken as confirmation of cefaclor allergy, although further confirmation with challenge testing was not done.

Skin prick and intradermal testing detect the presence of specific IgE bound to mast cells in skin. Their reliability is predicated on a history compatible with an IgE mediated reaction [24] and confirmation of negative results is made through provocation testing. While it is difficult to ascertain false positive IDT rates in those with reliable histories and index antibiotic positive skin tests, as these cases do not tend to go on to provocation testing to their respective index antibiotics, others have demonstrated the low predictive value of IDTs when used as general screening tools in those without a suspected antibiotic allergy.[25]

In contrast to penicillins, where studies have quantified the additional value of skin testing to penicillin side-chain specific determinants when investigating penicillin allergic patients,[26] the value of adding other cephalosporins (and which ones to add) when skin testing to the index cephalosporin has yet to be defined. The variability in cephalosporin skin testing outcomes can be attributed to several factors, including lack of standardisation of testing reagents, cephalosporin selection and the decline of cephalosporin skin test positivity over time. [21, 27]

There are no commercially available or validated reagents for skin testing in suspected cephalosporin allergy; testing is typically carried out using dilutions of parenteral solutions. This is problematic in that not all cephalosporins are available in parenteral form. We tested using cephalexin dissolved into an aqueous solution, but this had a high ratio of negative skin tests to positive drug provocation testing, indicating a poor positive predictive value (although 2 subjects had positive tests in the presence of a consistent history). It is likely that not all epitopes are reproduced in this preparation. Other studies have shown a higher sensitivity for cephalexin skin testing with different preparations.[28]

Testing to the index cephalosporin is necessary for confirmation since in some cases the allergy history can be refuted and the patient delabelled. Since this study was a retrospective audit, 16.3% of those suspected of an immediate allergy to cephalosporins were not tested to their index drug for clinical reasons. Hence confirmation or refutation of their allergy was missed. Confirmation of index drug allergy allows further investigation to define side chain cross-reactivity patterns [11, 19] or identify monosensitisation.

The loss of skin test positivity over time is less likely to have been the cause for false negative SPT and IDT results in our study, as most of the subjects deemed allergic to their index cephalosporins had their testing done within 5 years of their reaction. Furthermore, while 8 of the 24 allergic subjects were found positive on DPT despite negative skin tests, 6 of these were cephalexin allergic subjects making it more likely that poor sensitivity of skin testing to cephalexin due to incomplete epitope representation in the aqueous solution of the oral product used for testing, as previously explained.

While penicillin cross-reactivity can also result from side chain similarity, it is sensitization to the shared beta-lactam ring that is the basis of reactions that extend through multiple penicillins; more so, when side chains are dissimilar. Penicillins are chemically reactive due to a high degree of tension between the beta-lactam ring and the thiazolidine ring (*Figure 1*). As the ring opens, it forms major and minor antigenic determinants. Sensitisation to these determinants can be investigated through skin testing with PPL and MDM, respectively. In our cohort, all cephalosporin allergic subjects were tested for and found negative to these core beta-lactam antigenic determinants, highlighting the lack of beta-lactam cross-reactivity in this group. In contrast, in the largest study looking at cephalosporin allergy cross-reactivity patterns, 20 of 102 subjects (19.6%) were found to have

evidence of penicillin sensitisation on *in vitro* and skin testing. However, 11 of the 20 were deemed penicillin-sensitised via *in vitro* testing, and had negative penicillin skin tests; they were not challenged.[19] It is possible that these patients were not actually allergic to penicillin, as we had a similar finding in our cohort with 2 cefaclor-allergic subjects who also demonstrated *in vitro* sensitisation but had negative skin tests and tolerated an amoxicillin DPT. This has previously been shown in another study investigating penicillin allergic subjects, where sIgE positive but skin test negative subjects subsequently tolerated a penicillin DPT.[29]

Cephalosporoyl is a natural determinant resulting from the opening of the beta-lactam ring in cephalosporins; however, this structure is unstable and degrades with the rupture of the dihydrothiazine ring,[30] making it an unlikely antigenic determinant. Studies have shown that expulsion of the R2 side chain also occurs during this event.[30, 31] While some *in vitro* studies have suggested that the R2 side chain can potentially be an antigenic determinant, [32] the few reported cases were in cephalosporins that have similar R1 structural components as well.[33] Overall, this argues that the R1 side chain is the primary antigenic determinant in cephalosporin allergy, and therefore the more likely link to cephalosporin cross-reactivity.[30] The most common and significant side chain shared amongst several beta-lactams is the aminobenzene (or aminohydroxybenzene) found in the aminopenicillins amoxicillin and ampicillin, and aminocephalosporins such as cephalexin and cefaclor.

In our cohort, an R1-consistent side chain cross-reactivity pattern was seen in 2 out of the 4 cephalosporin allergic subjects with multiple sensitisations. Other studies have shown R1-similar cross-reactivity patterns to both cephalexin and cefaclor, as well as to other cephalosporin antibiotics not commonly used in Australia.[19, 34, 35] It is important to note that the side-chain is

not the exclusive epitope because only a small proportion of aminoccephalosporin-allergic individuals are allergic to other beta-lactams with the same or similar side-chains.[10]

One ceftriaxone-allergic subject was found to be sensitised to cephalixin as demonstrated by IDT, and a cefazolin-allergic subject was found to be allergic to cephalixin by DPT. Whilst this is not explicable by side-chain similarity, these subjects were not sensitised to other cephalosporins or penicillins, suggesting that these were examples of co-sensitisation rather than cross-reactivity by way of beta-lactam class effect. Other possibilities for cross-reactivity outside of R1 side chain similarity have also been proposed, including sensitisation to a part of the R1 side chain rather than the entire structure, sensitisation to a combination of both R1 and R2 structures, as well as sensitisation to steric variations among different cephalosporins.[19, 33, 36]

For those who are allergic to a cephalosporin, it is no longer enough to have a label of a “cephalosporin allergy”. The lack of cross-reactivity within cephalosporins, necessitates the identification of the specific index cephalosporin whenever possible, with application of a drug-specific label.[37] Accurately documenting the history and the results of cephalosporin allergy testing is key for delabelling.[38]

The main limitation in this study is its retrospective nature, with some variation in the cephalosporin panels used, depending on clinical indication. Furthermore, although we selected all cephalosporin allergic cases, the number of subjects allergic to each individual cephalosporin was relatively small, which is significant since we are asserting that each cephalosporin needs to be considered as an individual drug. As such, only limited conclusions can be drawn. Further prospective studies should be carried out with larger numbers of individuals. Nevertheless this work adds to the growing body of international literature and supports the emerging paradigm. The caveat is that whilst we did not

find evidence of a substantial risk of cephalosporin or beta-lactam cross-reactivity, cases have been reported and caution must still be exercised, particularly in the most severely allergic cases.

CONCLUSION

Cephalosporin allergy does not appear to be usually a class effect, with most cases in our cohort allergic only to their index cephalosporin. Co-sensitisation to other cephalosporins or penicillins was uncommon, and was usually based on side-chain cross-reactivity, in particular the amino group. However, beta-lactam panel testing is still recommended in severe (anaphylaxis) cases. *In vitro* testing is currently available only for cefaclor. *In vivo* skin testing with cephalosporins has not been well validated and so drug provocation testing remains the gold standard. Testing may be used to rule out allergy to the index drug and hence remove a drug allergy label, or to clear other structurally unrelated cephalosporins for use. There is a need for more robust assays which may be met by improved sIgE and basophil activation tests. Finally, the label “cephalosporin allergy” should not be used; rather the specific cephalosporin to which the patient is allergic should be the label.

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FIGURE LEGENDS**Figure 1. Beta-lactam structure**

1A. General structure of cephalosporins

1B. General structure of penicillin

Figure 2. Methodology**Figure 3. Suspected IgE mediated cephalosporin hypersensitivity**

TABLES

Table 1A. Dose concentrations of agents used for skin prick test (SPT) and intradermal test (IDT)

Test	Medication	Undiluted concentration (mg/ml)	Concentrations used (mg/ml)
SPT	MDM	0.5	0.5
	PPL	0.04	0.04
	Benzympenicillin	5	5
	Amoxicillin	20	20
	Cephalosporins*	3	3
IDT	MDM	0.5	0.005, 0.05, 0.5
	PPL	0.04	0.0004, 0.004, 0.04
	Benzympenicillin	5	0.05, 0.5, 5
	Amoxicillin	20	0.2, 2, 20
	Cephalosporins*	3	0.03, 0.3, 3

*Possible cephalosporins tested: cefaclor, cephalexin, cefazolin, ceftriaxone, cephalothin, cefotaxime, cefuroxime, ceftazidime, cefepime

Table 1B. Dose concentrations of agents used for drug provocation test (DPT)

Test	Medication	Therapeutic dose (mg)	Concentrations used (mg)	Route of administration
DPT	Cefaclor	500	5, 50, 500	oral
	Cephalexin	500	5, 50, 500	oral
	Cefazolin	1000	10, 100, 1000	intravenous
	Ceftriaxone	1000	10, 100, 1000	intravenous
	Cephalothin	1000	10, 100, 1000	intravenous
	Cefotaxime	1000	10, 100, 1000	intravenous
	Cefuroxime	500	5, 50, 500	oral
	Ceftazidime	2000	20, 200, 2000	intravenous
	Amoxicillin	500	5, 50, 500	oral
	Flucloxacillin	1000	10, 100, 1000	oral
	Piperacillin/Tazobactam	4000/500	40/5, 400/50, 4000/500	intravenous

Table 2. Demographics for suspected IgE mediated cephalosporin hypersensitivity

Characteristic	All subjects (n = 55)
Age (y), mean $\pm$ SD	49.9 $\pm$ 17.2
Women, no. (%)	37 (67.2)
Time (months) since last suspected cephalosporin reaction, mean	49.5
Manifestation, no. (%)	
Erythema	20 (36.3)
Urticaria	17 (30.9)
Angioedema	12 (21.8)
Bronchospasm	3 (5.4)
Nausea, vomiting and diarrhoea	5 (9)
Hypotension	9 (16.3)

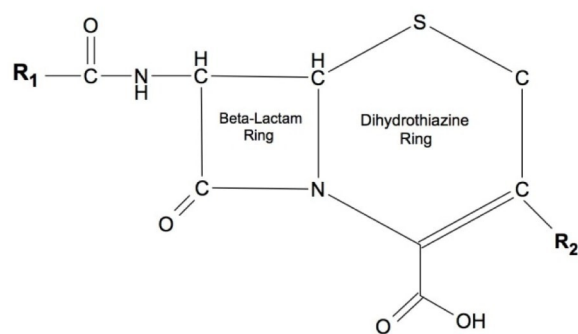
Table 3. Demographics, cephalosporin involved, index reaction, *in vitro* and *in vivo* test results of subjects found allergic to their index cephalosporin.

Sex	Age (y)	Cephalosporin involved	Type of reaction	CAP-IEIA (slgE)					Skin tests (SPT and/or IDT)						DPT challenged	DPT result
				PG	PV	AXy	AP	CCL	MDM	PPL	BP	AX	FLX	Cephalosporin/s (result/s)		
F	49	cefactor	A	<0.35	<0.35	<0.35	ND	1.18	-	-	-	-	-	CZL (-), CCL (-)	AX	-
M	85	cefactor	AN	0.53	0.48	0.56	0.52	1	-	-	-	-	-	CZL (-)	AX	-
F	44	cefactor	AN	<0.35	<0.35	<0.35	ND	0.59	-	-	-	-	-	CZL (-), CLX (-)	AX	-
F	20	cefactor	U	0.5	<0.35	<0.35	ND	34.4	-	-	-	-	ND	CZL (-), CLX (-)	AX	-
F	22	ceftriaxone	A	ND	ND	ND	ND	ND	-	-	-	-	-	CZL (-), CTX (-)	CTX	+
M	72	ceftriaxone	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CZL (-), CLX (-), CTX (+)	CLX	-
F	83	ceftriaxone	BS	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CZL (-), CTX (+)	ND	n/a
F	65	ceftriaxone	AN	<0.35	<0.35	<0.35	<0.35	ND	-	-	-	-	-	CZL (-), CLX (+), CTX (+)	ND	n/a
F	44	cephalexin	UA	<0.35	<0.35	<0.35	<0.35	<0.35	-	-	-	-	ND	CZL (-), CLX (-)	CLX	+
F	65	cephalexin	AN	ND	<0.35	0.82	ND	<0.35	-	-	-	+	ND	CZL (-), CLX (+)	ND	n/a
M	21	cephalexin	UA	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	ND	CZL (-), CLX (-)	CLX	+
M	66	cephalexin	E	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CLX (+)	FLX	-
M	59	cephalexin	E	<0.35	0.64	<0.35	ND	<0.35	-	-	-	-	ND	CZL (-), CLX (-), CTX (-)	CLX	+
M	32	cephalexin	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CZL (-)	CLX	+
F	59	cephalexin	E	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	ND	CZL (-), CLX (-), CTX (-)	CLX	+
F	48	cephalexin	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CZL (-), CLX (+)	ND	n/a
F	64	cephalexin	U	0.46	<0.35	10	ND	0.61	-	-	-	ND	-	CLX (-)	CLX	+
F	32	cephalothin	U	ND	ND	ND	ND	ND	-	-	-	-	-	CZL (-), CTX (-), CLT (+), CPM (-), CXM (-)	AX	-
M	50	cefazolin	AN	ND	ND	ND	ND	<0.35	-	-	-	-	ND	CZL (+), CLX (-)	CLX	-
F	60	cefazolin	UA	<0.35	<0.35	<0.35	<0.35	<0.35	-	-	-	-	-	CZL (-), CLX (-)	CZL + CLX	+
F	39	cefazolin	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	-	CZL (+)	AX	-
M	55	cefazolin	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	ND	CZL (+)	CLX	-
F	66	cefazolin	AN	<0.35	<0.35	<0.35	<0.35	ND	-	-	-	-	-	CZL (+)	ND	n/a
F	28	cefazolin	AN	<0.35	<0.35	<0.35	ND	<0.35	-	-	-	-	ND	CZL (+), CLX (-)	CLX	-

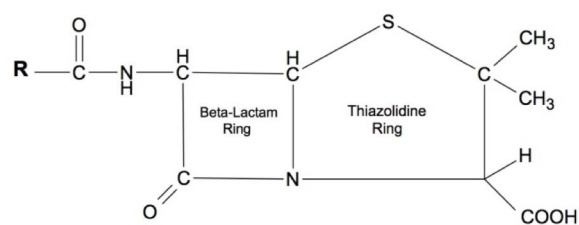
A, angioedema; AN, anaphylaxis; AP, ampicilloyl; AX, amoxicillin; AXy, amoxicilloyl; BP, Benzylpenicillin; BS, bronchospasm; CCL, cefactor; CLT, cephalothin; CLX, cephalexin; CPM, cefepime; CTX, ceftriaxone; CXM, cefotaxime; CZL, cefazolin; E, erythema; F, female; FLX, flucloxacillin; M, male; MDM, minor determinant mixture; n/a, not applicable; ND, not done; PG, penicilloyl G; PPL, penicilloyl-polylysine; PV, penicilloyl V; U, urticaria; UA, urticaria and angioedema

Table 4. Cephalosporin (green) and penicillin (orange) positive tests in cephalosporin allergic patients (yellow). * Co-sensitisation with index cephalosporin

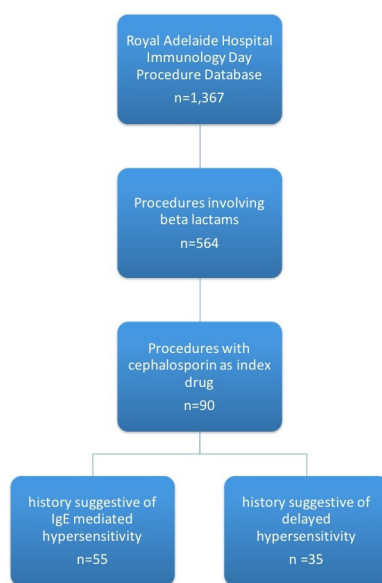
		Test cephalosporin: positive/total (%)							Test penicillin: positive/total (%)	
		Cephalexin	Cefazolin	Cephalothin	Cefaclor	Ceftriaxone	Cefotaxime	Cefepime	MDM/PPL	AMX
Index cephalosporin	Cephalexin (n=9)	9/9 (100)	0/7 (0)	–	1/9 (11.1)	0/2 (0)	–	–	0/9 (0)	2/9 (22.2)
	Cefazolin (n=6)	1/3 (33.3)*	6/6 (100)	–	0/5 (0)	–	–	–	0/6 (0)	0/6 (0)
	Cephalothin (n=1)	–	0/1 (0)	1/1 (100)	–	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
	Cefaclor (n=4)	0/2 (0)	0/4 (0)	–	4/4 (100)	–	–	–	0/4 (0)	0/4 (0)
	Ceftriaxone (n=4)	1/2 (50)*	0/4 (0)	–	0/2 (0)	4/4 (100)	–	–	0/4 (0)	0/4 (0)



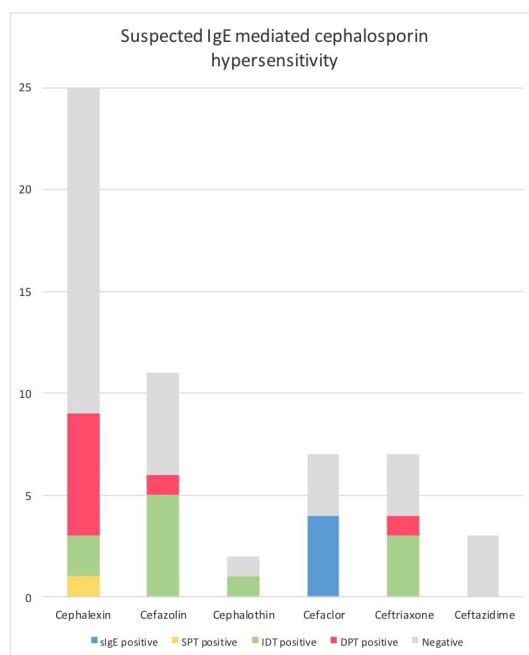
IMJ_14229_Figure 1A.jpg



IMJ_14229_Figure 1B.jpg



IMJ_14229_Figure 2.jpg



IMJ_14229_Figure 3.jpg