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Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime

Short title: Diagnosing perioperative hypersensitivity to cefuroxime

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Abstract

Introduction: The Danish Anaesthesia Allergy Centre (DAAC) investigated 89 adult patients with suspected perioperative cefuroxime-associated hypersensitivity reactions between 2004 and 2013. The goals were to determine if the time to index reaction after cefuroxime exposure could be used to implicate cefuroxime as the cause of the reactions and explore different test modalities in diagnosing cefuroxime hypersensitivity.

Method: Skin tests, in vitro tests, and titrated provocations were used to determine cefuroxime hypersensitivity. Patients were deemed cefuroxime positive on the basis of at least 2 positive tests and/or a positive provocation.

Results: One or more tests were positive for cefuroxime in 24/89 (27.0%) patients. One was only specific IgE-positive and was deemed cefuroxime negative. Twenty-three (25.8%) were deemed cefuroxime positive. There were 4 specific IgE-, 4 histamine release test-, 13 skin test-, and 14 provocation positive patients. There were 8 (34.8%) patients who were only provocation positive. Data on time to index reaction after cefuroxime exposure was available for 80 patients (22 in the positive group and 58 in the negative group), 22/22 (100%) of positive patients reacted in < 15 minutes versus only 38/58 (65.5%) of negative patients.

Conclusion: All patients with confirmed hypersensitivity to cefuroxime reacted within 15 minutes of administration, but so did 65.5% of cefuroxime negative patients, making timing of administration an unreliable predictor of causation in the perioperative setting.

Provocations were always positive when carried out in skin test positive patients; however 8 patients had positive provocations only, highlighting the need for provocation in skin test negative patients.

Abbreviations:

DAAC – Danish Anaesthesia Allergy Centre

SPT – Skin Prick Test

IDT – Intradermal Test

HR – Histamine Release

ASA – American Society of Anesthesiologist's classification

PPV – Positive predictive value

NPV – Negative predictive value

Introduction

Beta-lactam antibiotics are well known for causing IgE-mediated hypersensitivity reactions [1] and especially penicillins and cephalosporins are frequent causes of perioperative anaphylaxis [2,3]. As prophylactic antibiotics are usually administered at the time of induction of anaesthesia, the patient is exposed to several drugs and substances simultaneously. The anaesthesiologist often suspects the antibiotic, but it is not possible with certainty to determine the culprit drug at the time of reaction, thus postoperative investigation is necessary [4–6]. In Denmark patients with suspected hypersensitivity reactions during anaesthesia and surgery are investigated in the Danish Anaesthesia Allergy Centre (DAAC) and we have observed that the second-generation cephalosporin cefuroxime is the most frequently administered intravenous antibiotic in patients with suspected perioperative hypersensitivity reactions.

Investigation of allergy to antibiotics usually includes a combination of skin tests (skin prick test (SPT) and intradermal test (IDT)) [7,8] tests for specific IgE antibodies [9], histamine release tests (HR), and finally, drug provocation which is considered the “gold standard”[10]. Different test modalities have differing sensitivity and specificity, which have been examined for other drugs, but to our knowledge not for cefuroxime [9,11–14]. The aims of this retrospective study were: 1) to investigate how commonly cefuroxime is identified as the cause of perioperative hypersensitivity reactions in Denmark 2) whether timing of the administration of cefuroxime in relation to the reaction can be used to determine cefuroxime as the cause 3) To evaluate the different test modalities and their usefulness in diagnosing hypersensitivity to cefuroxime either alone or in combination.

Methods

Study population

Study subjects were adults (≥ 18 years), exposed to cefuroxime perioperatively. Out of the total of 413 patients investigated for suspected perioperative hypersensitivity reactions in DAAC between 2004 and 2013, a total of 98 patients had been exposed to cefuroxime. Nine were excluded (six were aged <18 and three did not complete all investigations) leaving 89 patients for inclusion.

Standard practice in DAAC is to test all drugs and substances the patient was exposed to using the following criteria: intravenous exposure < 1 hour before onset of reaction; or other exposures (oral, subcutaneous, local, epidural, spinal etc) < 2 hours before onset of reaction. Demographic data, clinical features of the reaction and DAAC-investigation results were retrieved from anaesthetic charts, referral forms and medical notes.

Patients were *post hoc* divided into two groups on the basis of the conclusion of investigations in DAAC using the following criteria for diagnosing hypersensitivity to cefuroxime: Patients with at least

2 positive tests and/or positive provocation, were deemed cefuroxime positive. Patients with negative provocation were deemed cefuroxime negative regardless of other test results.

As all data were collected as part of routine clinical investigations approval from an ethical committee was not required by Danish authorities.

Patient characteristics and clinical features

Patient characteristics such as age, gender, atopy status (defined as IgE sensitization to one or more common inhalant allergens i.e. positive Phadiatop® (Thermo Fisher Scientific, Uppsala, Sweden)), baseline serum tryptase, American Society of Anaesthesiologists classification (ASA),-clinical features of the reaction (severity, increase in serum tryptase at reaction compared with baseline, time from exposure to cefuroxime to first symptom, data on cancellation of surgery due to reaction) and severity of the reaction (class 1: Mild reactions with generalized cutaneous signs, self-limiting, class 2: Moderate, multiorgan involvement may be self-limiting, class 3: severe life threatening usually with multiorgan involvement, requires specific treatment class 4: cardiac arrest [5,6]) were collected and compared between the cefuroxime positive and cefuroxime negative group. For cefuroxime negative patients, data on whether another offending allergen was found were included.

Investigations/diagnostic tests

Blood samples for IgE and baseline tryptase analysis were drawn a median of 8 weeks (range 2-41 weeks), after the reaction. Skin tests were carried out a median of 12 weeks after the reaction for the whole group and a median of 11.5 and 13 weeks after reaction in skin tests negative and skin test positive patients respectively (data not shown). Standard procedure in DAAC is to carry out all tests in all patients, even if there is a positive result in another test modality. This is done after careful risk evaluation of the individual patient and if considered high risk, we will accept two or

more positive tests and abstain from provocation and in some cases intradermal test in such patients.

Serum tryptase was measured using the ImmunoCAP® system (Thermo Fisher Scientific, Uppsala, Sweden). Tryptase was measured in a sample from the time of reaction (ideally taken 1- 4hrs after the reaction) and always compared to the patient's own baseline taken several weeks later [15].

Specific IgE for cefuroxime was measured using the ImmunoCAP® method, Thermo Fisher Scientific, Uppsala, Sweden. The specific assay was available for research only and cefuroxime was coupled to a Poly-lysine backbone, which was then coupled to the solid phase of the ImmunoCAP®. Values >0.35 kUA/l were considered positive.

Histamine release test was carried out by RefLab, Copenhagen [16]. It measures the degree of basophil degranulation in response to stimulation with a specific allergen. A positive result is given as a reaction class (1-12) basically describing the titre of cefuroxime giving a positive reaction. HR classes 1 and above were considered positive.

Some patients are non-releasers i.e. no basophil histamine release is seen on stimulation with the positive control (Anti-IgE) and thus reaction on stimulation with an allergen cannot be expected. Results in these patients are inconclusive.

Skin prick tests were carried out in duplicate on the forearm with cefuroxime 0.5 mg/ml, 5.0 mg/ml and 50 mg/ml (undiluted), negative control with saline and positive control with histamine. Development of a wheal ≥ 3 mm in diameter after 20 minutes was considered positive.

Intradermal tests were carried out in duplicate on the back with cefuroxime 0.05 mg/ml and 0.5 mg/ml (1:100 of vial concentration), negative control with saline. Two procedures have been used. From 2004-2010 a bleb of 3-5 mm was produced without regard for injected volume. Since January 2011 a fixed volume of 0.02 ml were used. An increase in diameter to $\geq$ twice the diameter of the

negative control or an increase in diameter of the initial bleb of ≥ 3 mm at 20 minutes was considered positive. [14,17,18]

In one case with a very severe clinical reaction (cardiac arrest), positive HR test (class 12) and strongly positive skin prick tests (7 mm wheal on 0.5 mg/ml and clear dose response on increasing concentrations) the IDT was considered too high risk and thus not performed.

Drug provocation. A titrated three step intravenous provocation was performed with increasing doses of cefuroxime; 7.5 mg, 75 mg and maximum dose of 650 mg with 30-minute interval between doses. The patient was observed 2 hours after last dose. Objective symptoms from the skin such as erythema and urticaria were considered reliable signs and provocation was stopped when symptoms arose. If the patient experienced subjective symptoms only e.g. itching, provocation was continued until objective symptoms appeared or final dose was reached.

In 6 cases, where the symptoms of the initial reaction were severe and at least two other test modalities (SPT, IDT, IgE or HR) were positive, provocation was not performed.

Statistics. Descriptive and ordinal data were analysed using SigmaPlot (Systat Software inc, USA). Ordinal data were analysed with Mann-Whitney Rank Sum Test. Correlation analyses were made using SigmaPlot, Spearman Rank Order Correlation. Categorical data were analysed using Excel (Microsoft, USA) with ChiSquare Test. P-values < 0.05 were considered significant.

Results

Cefuroxime hypersensitivity was identified as the cause in 23 out of 413 (5.6%) suspected perioperative allergic reactions investigated in DAAC from 2004 to 2013. A total of 98 patients (23.7%) had been exposed to cefuroxime. In this study 23 out of 89 (25.8%) included patients were diagnosed with hypersensitivity to cefuroxime defined as positive provocation, or if provocation was

not performed, at least two other positive tests. Consequently, 66 (74.2%) patients tested negative for cefuroxime, and for 27 (40.9%) of those, another allergen was found: chlorhexidine 7, oxytocin 5, patent blue 4, chlorhexidine and penicillin 1, latex 2, other cause 8.

Patient characteristics and clinical features are listed in table 1.

The two groups did not differ significantly on age, atopy status, timing of sampling of serum for measurement of reaction tryptase or level of baseline tryptase. There were significantly more men in the positive group. Reactions were more severe in the positive group (60.9% and 21.7% class 3 and 4 respectively vs 42.4% and 1.5% class 3 and 4 in the negative group, $p<0.001$). Of the 39 patients in the negative group where no allergen was found 28.2% had a class 1 reaction, 33.3% class 2 and 38.5% a class 3 reaction (data not shown). The difference between reaction tryptase and baseline (Δ tryptase) was significantly greater in the positive group than in the negative (median 17.8 vs -0.2 $\mu\text{g/l}$, $p<0.001$). There was a moderate positive correlation between reaction class and Δ tryptase (correlation coefficient of 0.55, $p=0.001$). The surgical procedure was cancelled due to the reaction more often in the positive group (43.5% vs 13.6%, $p=0.003$).

Time between administration of cefuroxime and reaction (fig. 1) was significantly shorter in the positive group median 5 min (IQ range 2-10min) vs median 15 min (IQ range 5-25) in the negative group ($p<0.001$)

Only 80 (22 positive and 58 negative) patients were included in analyses of time from administration to reaction. One patient in the positive group was missing data and 8 patients from the negative group were excluded due to missing data. All 22 (100%) patients from the positive group reacted within 15 minutes of intravenous cefuroxime administration, and in the negative group 38/58 (65.5%) reacted within 15 minutes. Out of these, another allergen was found in 15 cases and no allergen was found in 23 cases.

In total 24 patients had one or more positive tests and investigation results are shown in table 2.

Only 23 patients fulfilled the criteria for hypersensitivity to cefuroxime.

Specific IgE for cefuroxime was elevated in 5 patients. However, one patient was thought to have a false positive result on specific IgE as provocation and all other tests results were negative. She was therefore included in the cefuroxime negative group for analyses concerning clinical features.

Seventeen patients had a positive provocation test. Six patients did not have provocation test performed, due to very severe initial clinical reactions (cardiac arrest/circulatory insufficiency) and /or two or more positive tests.

Eight patients (34.8%) were positive only on provocation. Thirteen patients had positive skin testing and in 7 of these a subsequent provocation was also positive. Two of the skin test positive patients also had a positive specific IgE.

All of the 13 skin test positive patients had a positive SPT and 9 also had a positive IDT. In one case IDT was not performed due to a strongly positive SPT, and in one case the result was inconclusive.

Thus in 2 patients with a positive SPT the IDT was negative. There was no correlation between maximal wheal diameter of SPT and reaction class (correlation coefficient -0.08, $p=0.79$) or between maximal wheal diameter and Δ tryptase (correlation coefficient 0.26, $p=0.40$) in the positive group.

All of the 66 patients concluded to be negative to cefuroxime tested negative on skin testing (SPT or IDT or both), ie there were no false positive skin tests.

Four patients had a positive HR test, and all four had positive SPT and very severe initial reactions (3 cardiac arrests and one a class 3 reaction). Four patients were non-releasers, making results inconclusive.

Table 3 shows sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each of the diagnostic test modalities.

Discussion

Over the 9-year period from May 2004 through May 2013, there were approximately 3,6 million anaesthetics performed in Denmark [19]. A total of 413 patients were investigated for suspected perioperative allergic reactions in DAAC in the same period and 23.7% of them had been exposed to cefuroxime.

Cefuroxime was identified as the cause of reactions in 23 out of 89 (25.8%) exposed patients and overall accounted for 5.6 % of the reactions in the 413 patients investigated for suspected perioperative allergic reactions, making it one of the most common single drugs causing perioperative hypersensitivity in Denmark.

The majority of reactions were severe and 19/23 (82.6%) in the cefuroxime positive group met the current working definition for anaphylaxis (reaction class 3 and 4). Using a perioperative exposure rate of 23.7%, this leads to a calculated incidence of perioperative cefuroxime-associated anaphylaxis of 1 in 44,905 exposures during the study interval. Beta-lactam antibiotics are known to cause perioperative reactions in other countries [2,20] and the profile of the specific drugs incriminated largely reflects differences in the patterns of use in the respective countries.

In this study we have shown that there is a clear temporal connection between exposure to intravenous cefuroxime and onset of symptoms as all patients in the cefuroxime positive group reacted within 15 minutes of exposure (median 5 minutes). This means that the likelihood of cefuroxime being the allergen diminishes when reactions occur later than 15 minutes after cefuroxime administration. Importantly, 65.5% of patients testing negative to cefuroxime also reacted within 15 minutes of cefuroxime administration. Therefore a reaction should never be attributed to cefuroxime without systematic investigation of all drugs and substances the patient was exposed to. Such a conclusion could either lead to over-diagnosing cefuroxime hypersensitivity in patients with no hypersensitivity or to suspecting the wrong allergen in patients where other causes than cefuroxime might have been found, if searched for. In fact, in the cefuroxime negative

group, 27 patients had another allergen found on investigation. For the remaining 39 patients in the negative group the reactions may be explained by non-specific direct histamine release induced by drugs such as opioids or even a non-allergic differential diagnosis eg bleeding, relative hypovolaemia from regional blockade, other types of shock, poorly treated asthma, angioedema from ACE inhibitors [6]. Patients in the negative group had significantly lower severity grades ($p<0.001$) and Δ tryptase ($p<0.001$) than the positive group. This can be explained by the heterogeneity of the negative group including 27 patients where another culprit allergen was found and 39 where no allergen was identified.

Five patients had a positive specific IgE to cefuroxime, of which one was deemed false positive. The sensitivity for specific IgE was 17.4%, specificity 98.5% and PPV 80%. The tendency for IgE measurements for cephalosporins to show low sensitivity has been described previously in several studies [9,21,22]. The general problem of low sensitivity of IgE assays for cephalosporins has been linked to the lack of knowledge about the allergenic determinants of cephalosporins [23–25].

A low sensitivity (22.2 %) was also seen for HR.

In the ImmunoCap® system the only cephalosporin test commercially available is IgE to cefaclor, but we have had access to a non-validated research version of specific IgE to cefuroxime which may explain the low sensitivity found with this assay.

Two patients with positive SPT had a negative IDT. There are no cases of positive IDT and negative SPT, so in this study the SPT has a higher sensitivity (56.5% vs. 42.9%). There are two possible explanations for this 1) The maximal concentration for IDT used in our investigations was 0.5 mg/mL which had been used in DAAC since we started investigations in 1999. However, this is lower than the 1-2 mg/mL which is recommended in other studies and guidelines [2,7,17]. As a consequence we have now increased our highest concentration to 5mg/ml (if SPT and lower concentrations on IDT

are negative) to be more in line with international recommendations. Time will show whether this will increase the sensitivity of IDT with cefuroxime in our centre, and possibly decrease the rate of patients testing positive on provocation only. Also, diagnostic criteria for IDT have since been revised in our centre due to findings of low sensitivity of our previously used positivity criteria of diameter of wheal $\geq$ twice the diameter of negative control [14].

The concentration used in SPT (50 mg/mL) is higher than recently recommended [17], but in our study all 66 patients in the cefuroxime negative group tested negative on this concentration (PPV 100%) which must therefore be considered reliable and non-irritative.

Achieving the highest possible sensitivity and specificity is important in allergy investigations to ensure the correct allergen is identified and to avoid warnings against harmless agents. No single test fulfills these criteria and thus several test modalities are often combined, as also shown in other studies [26]. Drug provocation is thought to be the Gold Standard, but we have not been able to find studies investigating provocation in skin test positive patients. Due to the resulting lack of evidence of sensitivity and specificity of skin testing for most drugs, we carry out careful titrated provocation even if skin tests are positive when investigating patients in DAAC. Each case is individually risk assessed and if clinical reactions were very severe and two or more of skin test results and/or in vitro test results are strongly positive, provocation will not be performed. One study investigated the predictive values of skin testing with different cephalosporins (not including cefuroxime) in patients with no clinical suspicion of hypersensitivity [27]. Low sensitivity and specificity of skin testing were found, suggesting that skin testing is less useful for predicting immediate hypersensitivity to cephalosporins in the absence of clinical suspicion of hypersensitivity. However, the probability of a true positive test is very low in an unselected population compared to our population of 89 patients presenting with perioperative hypersensitivity reactions and known exposure to cefuroxime with an incidence of cefuroxime hypersensitivity of 25.8%. In fact, we found no false positive results on either SPT or IDT with cefuroxime in patients with a relevant clinical history giving a specificity and

PPV of 100%. On the other hand all 7 patients with positive SPT who had provocation performed were positive on provocation at quite low doses ie first or second dose, see table 2.

This has led us to conclude that positive skin tests, especially SPT, with cefuroxime are reliable and we no longer perform provocation in patients with positive SPT. In SPT positive patients IDT will now only be performed if no other test modalities are positive (IgE or HR), as a minimum of 2 positive tests has been shown to increase the likelihood of true positive testing [13,14]. As we have recently increased the maximum concentration used on IDT we will likely continue to carry out carefully titrated provocation in patients who are SPT negative, but positive on IDT only on the highest concentration. This will help identify if the positive test is a true positive or perhaps a toxic reaction on the higher concentration. Very importantly, eight patients tested negative in all other tests than provocation. Interestingly these patients mostly reacted on the second dose or full dose. These patients did not differ from the other hypersensitive patients in their clinical presentation and would have been overlooked if our investigation protocol did not include provocation. Several studies have previously identified skin test negative patients who tested positive on provocation for different beta-lactam antibiotics, but none of these studies look at cefuroxime or perioperative hypersensitivity [9,21,26,28]. In this study of patients with perioperative hypersensitivity reactions, we show that a relatively large proportion of patients (34.8%) reacting to cefuroxime test negative on all tests except intravenous provocation. In our centre we always aim to carry out provocation using the route of administration from the reaction. In the perioperative setting cefuroxime is always given iv and in Denmark oral cefuroxime is only very rarely used. Therefore we cannot comment on whether oral provocation with cefuroxime would have led to the same results.

The discrepancy between test results raises the question whether the mechanism in skin test negative patients is actually IgE-mediated. However, clinical symptoms in the skin test negative patients resemble immediate hypersensitivity reactions, and more than half of the patients had an increase in serum tryptase at the time of reaction suggestive of mast cell degranulation. Differences

in epitopes, binding affinity or different mechanisms of mast cell activation such as by the complement system or by direct activation of mast cell by drugs such as opioids may account for the variation in investigation results but further studies would be needed to elucidate this.

In conclusion the perioperative setting is very complex and we recommend that patients with suspected perioperative hypersensitivity reactions undergo systematic allergological investigation including all drugs and substances they were exposed to. Timing of drug administration in relation to the reaction is not a good predictor of causation. Also due to the low sensitivity and relatively high specificity of the individual tests used in allergy testing we advocate using a combination of several test modalities to increase sensitivity. Also we recommend always to perform drug provocation when other tests are negative or inconclusive.

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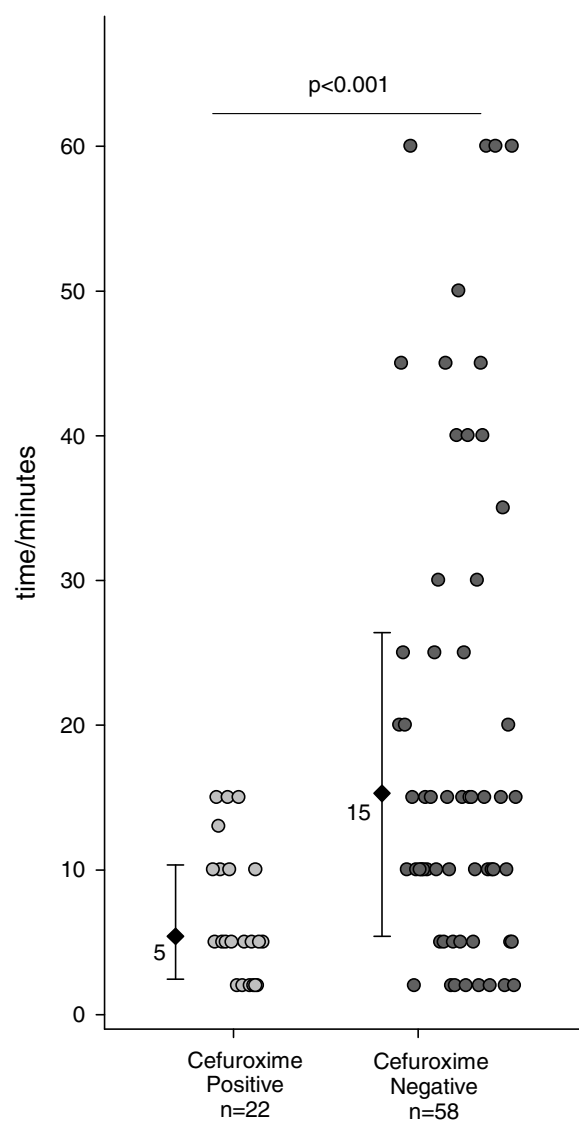


Figure 1: Time from administration of iv cefuroxime to onset of reaction for positive and negative group (Median, IQ range).

Table 1
Data from all patients tested for cefuroxime n=89

	All patients	Cefuroxime Positive	Cefuroxime Negative	p§	p#
Whole group n (%)	89 (100)	23 (25.8)	66 (74.2)		
Age years					
Median (min-max)	53 (18-84)	57 (21-75)	46 (18-84)	p=0.093	
Sex n (%)					
Female	57 (64.0)	10 (43.5)	47 (71.2)		p=0.017
Male	32 (36.0)	13 (56.5)	19 (28.8)		
Phadiatop n (%)					
<0.35	50 (56.2)	10 (43.5)	40 (60.6)		p=0.171
>0.35	33 (37.1)	11 (47.8)	22 (33.3)		
Not available	6 (6.7)	2 (8.7)	4 (6.1)		
Surgery completed n (%)					
Yes	70 (78.7)	13 (56.5)	57 (86.4)		p=0.003
No	19 (21.3)	10 (43.5)	9 (13.6)		
Reaction class n (%)					
1	17 (19.1)	1 (4.3)	16 (24.2)		p<0.001
2	24 (27.0)	3 (13.0)	21 (31.8)		
3	42 (47.2)	14 (60.9)	28 (42.4)		
4	6 (6.7)	5 (21.7)	1 (1.5)		
Symptoms n (%)					
Skin	84 (94.4)	22 (95.7)	62 (93.9)		p=0.759
Circulatory	68 (76.4)	21 (91.3)	47 (71.2)		p=0.051
Respiratory	30 (33.7)	11 (47.8)	19 (28.8)		p=0.096
Reaction level tryptase					
µg/L, Median (IQ range)	9.7 (3.4-22.0)	20.6 (12.1-41.1)	5.3 (2.7-12.8)	p<0.001	
Time from reaction to tryptase					
Hours, Median (IQ range)	2 (1-2)	1.5 (1-2)	2 (1-3)	p=0.636	
Baseline tryptase					
µg/L, Median (IQ range)	4.3 (3.0-6.2)	4.9 (3.4-6.5)	4.1 (3.0-5.8)	p=0.228	
Δ Tryptase for reaction class					
µg/L, Median (IQ range)					
1	-1.2 (-1.7- -0.7)	-1.07	-1.3 (-1.7- -0.6)		
2	-0.1 (-0.7-2.1)	8.4 (3.4-12.5)	-0.4 (-1.1-1.0)		
3	10.3 (-0.6-19.2)	18.0 (5.1-23.5)	8.0 (-0.8-15.6)		
4	63.0 (44.3-84.7)	74.5 (35.0-85.5)	51.5		
Whole group	1.1 (-1.1-16.9)	17.8 (5.7-30.5)	-0.2 (-1.4-8.2)	p<0.001	
Time from adm to reaction*					
Minutes, Median (IQ range)	10 (5-17.5)	5 (2-10)	15 (5-25)	p<0.001	

§ Mann-Whitney Rank Sum Test

Chi2Test

*8 patients from the negative group and 1 patient from the positive group were excluded from this calculation. see results section for details

Reaction class:

1: Mild reactions with generalized cutaneous signs, self-limiting

2: Moderate, multiorgan involvement may be self-limiting

3: Severe life-threatening usually multiorgan involvement, requires specific treatment

4: Cardiac arrest

Table 2
Data from all patients with at least one positive test for cefuroxime n=24.

Sex	Age years	Reaction Class	Time from drug to reaction (minutes)	Reaction tryptase ($\mu\text{g/L}$)	Δ tryptase (reaction -baseline tryptase)	IgE (kU/L)	HR	SPT (wheal, mm*)	IDT (control / reaction, mm**)	Provocation (dose giving symptoms***)
<i>Patients diagnosed with hypersensitivity to cefuroxime n=23</i>										
m	43	2	5	5.31	1.57	Neg	ND	Neg	Neg	Pos (525 mg)
m	61	3	15	24.7	19.36	Neg	Neg	Neg	Neg	Pos (500 mg)
f	33	3	NA	20.3	18.27	Neg	Neg	Neg	Neg	Pos (650 mg)
f	21	1	10	1.24	-1.07	Neg	Neg	Neg	Neg	Pos (250/75 mg)
m	56	3	5	113	104.97	Neg	NR	Neg	Neg	Pos (75 mg)
f	38	3	15	ND	ND	Neg	Neg	Neg	Neg	Pos (650/75 mg)
m	60	3	5	11.4	-2.1	Neg	Neg	Neg	Neg	Pos (300/75 mg)
f	57	3	2	15.5	9.37	Neg	Neg	Neg	Neg	Pos (75/7.5mg)
m	60	3	5	30.8	25.83	Neg	class 9	7	IC	Pos (7.5 mg)
m	48	4	5	91.2	84.67	Neg	class 4	4	3 / 8	ND
f	51	4	2	12.3	7.08	Neg	class 7	4	3 / 8	ND
m	68	4	2	94.3	88.17	Neg	class 12	9	ND	ND
m	54	2	2	20.6	13.74	Neg	NR	5	6 / 17	ND
m	75	4	2	47.3	44.32	Neg	Neg	11	9 / 21	ND
m	32	3	5	39	17.8	Neg	Neg	6	3 / 10	Pos (7.5 mg)
m	57	3	5	ND	ND	Neg	NR	9	8 / 22	Pos (7.5 mg)
f	43	3	5	17.7	14.08	Neg	Neg	3	6 / 10	Pos (300/75 mg)
f	70	3	13	2.2	-1.49	Neg	Neg	5	Neg	Pos (4.5 + 3mg)
f	58	3	15	27.3	22.68	Neg	Neg	4	Neg	Pos (75 mg)
f	64	4	10	79.4	74.48	0.44	NR	5	7 / 11	ND
m	64	2	2	13.4	8.74	17.5	Neg	10	7 / 13	Pos (2.5 mg)
f	67	3	10	4.2	0.88	0.41	Neg	Neg	Neg	Pos (650/7.5 mg)
m	66	3	10	36	24.3	1.55	Neg	Neg	Neg	Pos (650 mg)
<i>Patients NOT diagnosed with hypersensitivity to cefuroxime n=1</i>										
f	45	2	15	NA	NA	0.8	Neg	Neg	Neg	Neg (650 mg)

ND: not done; NA: not available; NR: non-releaser; IC: inconclusive; NE: not exposed

*max wheal diameter at conc 50mg/ml

**max wheal diameter control/ reaction at conc 0.5mg/ml

***when 2 doses noted, smaller dose produced subjective symptoms only; larger dose produced objective symptoms

Table 3

Sensitivity, specificity, PPV and NPV for each diagnostic test modality*

	Sensitivity	Specificity	PPV	NPV
IgE	17.4%	98.5%	80%	77.4%
HR	22.2%	100%	100%	82.5%
SPT	56.5%	100%	100%	86.8%
IDT	42.9%	100%	100%	84.6%

PPV: positive predictive value, NPV: negative predictive value

*Allergy was defined as positive provocation or at least two other positive tests

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Conflicts of interest

In order of this manuscript, all authors declare that there are no conflicts of interest.