

Specific IgE to cefazolin: Does it benefit diagnosis?



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Clinical Implications

- This is the first study to investigate the clinical value of a specific IgE (sIgE) to cefazolin in reactive patients and uneventfully exposed control individuals. The sIgE/total IgE ratio has a good predictive value and can be useful in diagnosing cefazolin allergy.

TO THE EDITOR:

Cefazolin is a first-generation cephalosporin antibiotic mainly used in perioperative prophylaxis. It is one of the major causes of perioperative anaphylaxis with serious consequences of misdiagnosis. In our series, antibiotics, mainly cefazolin, constitute the third cause of perioperative anaphylaxis.¹ For the moment, diagnosis predominantly relies on skin testing² and if possible a basophil activation test (BAT).³ However, the sensitivity and specificity of these tests are not absolute, and BAT, for the time being, has not entered mainstream application as it requires experienced personnel and specific equipment.⁴ Therefore, as intravenous drug challenges (iv-DC) are hampered by ethical and logistic issues, the availability of a new, safe, and reliable *in vitro* diagnostic could be of interest to add to the diagnostic algorithm.

This study aims at exploring the clinical utility of specific IgE (sIgE) to cefazolin. As it is known that specificity of an sIgE assay might be influenced by values of total IgE (tIgE),⁵ the usefulness of an sIgE cefazolin/tIgE ratio is evaluated. Furthermore, because sensitivity of β -lactam sIgE tests is known to decrease over time,⁶ a longitudinal follow-up was performed.

This is a retrospective observational study. A total of 43 patients, of whom 39 had a positive cefazolin skin test and 4 a negative cefazolin skin test but positive iv-DC with cefazolin, and 31 control individuals who had a negative skin test result and who tolerated an iv-DC with cefazolin, were included via the outpatients' clinics of allergology of the Antwerp University Hospital between April 2006 and March 2018. The large majority of patients and control individuals had experienced a perioperative hypersensitivity reaction, mainly anaphylaxis.¹ The local ethics committee approved this study (B300201524055) and patients provided an informed consent in accordance with the Declaration of Helsinki.

Skin testing with cefazolin (Cefazolin 1 g; Sandoz, Vilvoorde, Belgium) was performed according to the European Network for

Drug Allergy guidelines,⁷ but since 2013, a maximum nonirritating concentration of 20 mg/mL was applied as described in this journal by our group.² As our patients were defined by a positive cefazolin skin test or a positive iv-DC and the control individuals having both a negative skin test and a negative iv-DC, we think that the change of skin test concentration is unlikely to be a limitation for this study.

All participants with negative skin testing had an iv-DC with cefazolin. Eight incremental doses of cefazolin starting from 1 mg up to a cumulative dose of 1000 mg were administered. The updosing interval was predefined at 15 minutes. After the last dose, patients were kept under close observation for at least 2 hours. A challenge test was only considered positive when objective symptoms could be observed. One could argue that an 8-step challenge might lead to desensitization. However, the start dose of 1 mg is likely to be too high for a desensitization protocol and 5 of our 31 exposed control individuals were uneventfully re-exposed to cefazolin after a median time interval of 2.8 (0.1-12.0) months. Therefore, desensitization is highly unlikely.

tIgE and sIgE to cefazolin were measured using an ImmunoCAP system FEIA (Phadia Thermo Fisher, Uppsala, Sweden) according to the manufacturer's instructions. An sIgE to cefazolin solid phase assay was developed and kindly provided by Phadia Thermo Fisher. The cefazolin ImmunoCAP, for research use only, was produced with a cephalosporin conjugate covalently bound to the cellulose solid phase through poly-lysine as carrier protein. The method to provide the cefazolin conjugate involves a nucleophilic attack of the β -lactam ring under alkaline conditions. sIgE to cefazolin and tIgE were measured on stored sera obtained before skin testing with cefazolin and as a consequence also before the iv-DC. The detection limit for sIgE cefazolin was 0.10 kUA/L. tIgE values were missing in 2 patients. The sIgE/tIgE ratio was calculated by dividing sIgE cefazolin through tIgE. sIgE cefazolin values below 0.10 kUA/L were arbitrarily set at 0.01 kUA/L. Decision thresholds were set according to the recommendations of the manufacturer or specific thresholds were calculated using 2-graph receiver-operating curves (ROC).

In the patients, the median (range) for sIgE cefazolin was 0.14 (<0.10-0.93) kUA/L and this was not significantly different from that in the control individuals, 0.01 (<0.10-0.68) kUA/L ($P > .05$, Mann-Whitney U test) (Figure 1, A). Therefore, no drug-specific threshold was calculated. In the patients, the median (range) for tIgE was 53 (6-796) kU/L and was significantly lower than that in the control individuals, 117 (8-1270) kU/L ($P < .05$, Mann-Whitney U test) (Figure 1, B). A moderate correlation between tIgE and sIgE cefazolin was found ($r = 0.437$, Spearman rank correlation). As displayed in Figure 1, C, the sIgE/tIgE ratio was calculated and was significantly higher in the patients as compared with the exposed control individuals ($P < .05$, Mann-Whitney U test). ROC analysis revealed a cutoff ratio of 1.42×10^{-3} to be most discriminative between patients and control individuals. For this threshold, a sensitivity of 49% and a specificity of 94% were found (Figure 1, D). These are very good results compared with sIgE assays, not corrected for the tIgE, to other

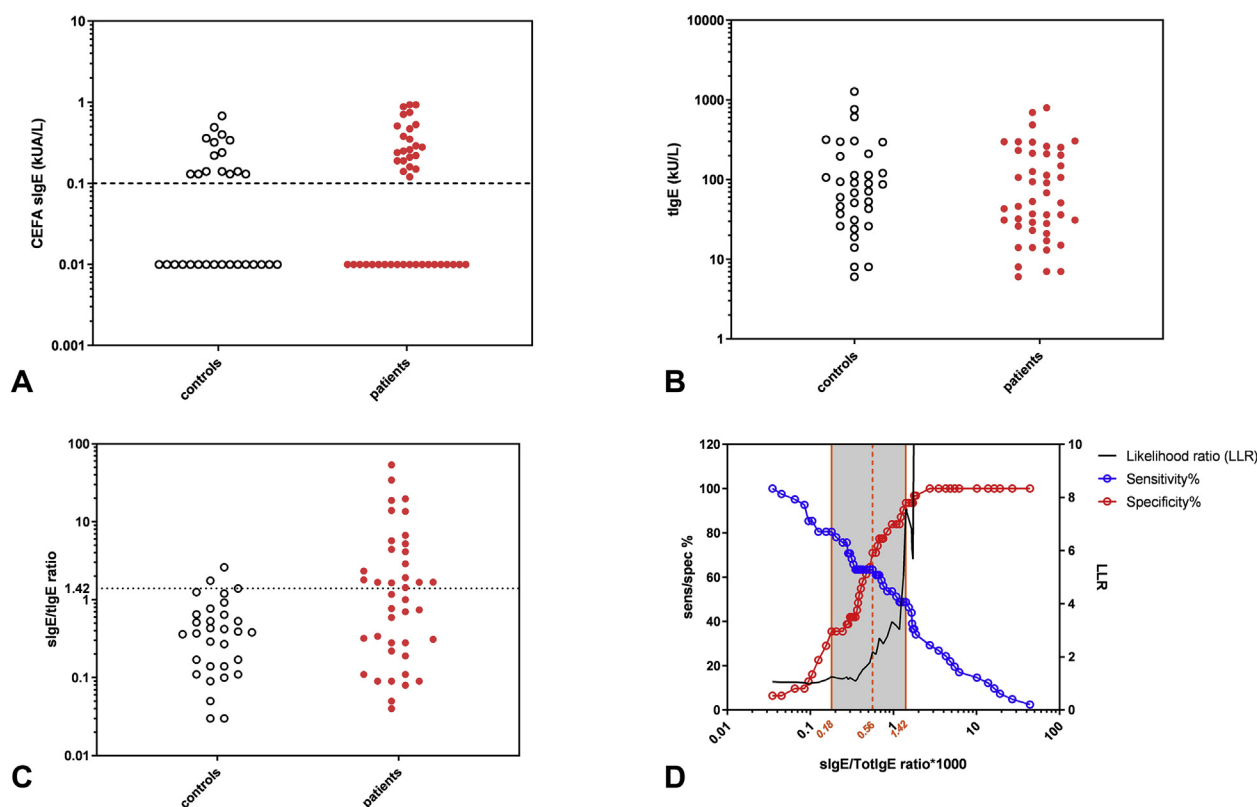


FIGURE 1. **A**, Specific IgE (sIgE) values to cefazolin in exposed control individuals (open circles) and patients (closed circles). The detection limit for sIgE cefazolin was 0.10 kUA/L (dashed line). Values below the detection limit were set at 0.01 kUA/L. **B**, Total IgE (tIgE) values in patients and controls. **C**, sIgE/tIgE ratio values in patients and controls. The dashed line indicates the 2-graph receiver-operating characteristic—calculated decision threshold for positivity (1.42×10^{-3}) (**D**). *CEFA*, Cefazolin; *sens*, sensitivity; *spec*, specificity.

TABLE I. Test results in patients with a positive baseline sIgE/tIgE ratio value

Patient	Time interval (y)	Skin test		sIgE cefazolin (kUA/L)		tIgE (kU/L)		sIgE/tIgE	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
1	5.8	+ (IDT 2 mg/mL)	+ (IDT 2 mg/mL)	0.24	<0.10	7	9.8	34.29×10^{-3}	1.02×10^{-3}
2	4.3	+ (IDT 0.2 mg/mL)	+ (IDT 0.2 mg/mL)	0.16	<0.10	28	19	5.71×10^{-3}	0.53×10^{-3}
3	2.6	+ (IDT 0.2 mg/mL)	+ (SPT 20 mg/mL)	0.38	<0.10	232	142	1.64×10^{-3}	0.07×10^{-3}
4	4.8	+ (IDT 2 mg/mL)	—	0.53	<0.10	294	47	1.80×10^{-3}	0.21×10^{-3}
5	8.4	+ (SPT 200 mg/mL)	+ (IDT 2 mg/mL)	0.51	<0.10	26	7.28	19.62×10^{-3}	1.37×10^{-3}
6	6.3	+ (IDT 2 mg/mL)	—	0.93	<0.10	484	312	1.92×10^{-3}	0.03×10^{-3}
7	7.5	+ (SPT 20 mg/mL)	+ (IDT 2 mg/mL)	0.19	<0.10	43	25	4.42×10^{-3}	0.40×10^{-3}

+, Positive; —, negative; *IDT*, intradermal testing; *SPT*, skin prick testing.

Overview of skin test, specific IgE (sIgE) to cefazolin, total IgE (tIgE), and sIgE/tIgE ratio results in patients with a positive baseline sIgE/tIgE ratio value ($\geq 1.42 \times 10^{-3}$) at baseline and at follow-up. For calculation of the sIgE/tIgE ratio, sIgE values below the detection limit (0.10 kUA/L) were set at 0.01 kUA/L.

β -lactam antibiotics, as sensitivity and specificity usually vary between 0% and 85% and 52% and 100%, respectively.⁵ The potential added value of an sIgE/tIgE ratio for β -lactam antibiotics (penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl) was also already addressed by Vultaggio et al.⁸ In their study,⁸ β -lactam sIgE/tIgE ratio values $\geq 2 \times 10^{-3}$ yielded a specificity of 95% and a sensitivity of 43.3%, comparable with our results. However, the sIgE/tIgE ratio was negative in our 4 patients with a negative cefazolin skin test and positive iv-DC.

As it is known that sIgE to β -lactam antibiotics decreases over time,⁶ we set up a follow-up study that intended to re-evaluate all patients who demonstrated a positive sIgE/tIgE ratio. Finally, 7 of those patients were willing to have repeated skin testing with cefazolin and quantification of tIgE and sIgE to cefazolin. The median time interval between initial evaluation and follow-up testing was 5.8 (2.6–8.4) years. As displayed in Table I, the sIgE/tIgE ratio turned negative in all patients. This observation was due to a decrease in sIgE cefazolin and not to an increase in tIgE (Table I). In contrast to sIgE, unlike skin testing for other

cephalosporins,⁹ the cefazolin skin test remained positive in 5 of 7 of these patients.

This is the first study to explore the clinical value of an sIgE to cefazolin. The sIgE/tIgE ratio has a good positive predictive value. However, it does not seem to substitute skin testing and sensitivity seems to drop in time. For the time being, skin testing with cefazolin still merits the status for primary diagnostic testing and cannot be substituted by sIgE nor sIgE/tIgE.

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