

Immediate Reactions to Cephalosporins: It is Time to Standardize the Diagnostic Essence



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A recent European survey discloses cephalosporins to account for 10% to 40% of β -lactam hypersensitivity reactions, with ceftriaxone, cefaclor, and cefuroxime most commonly involved.¹ Of the 333 cases of drug-induced anaphylaxis registered in Europe between 2002 and 2010, 12.3% were attributable to cephalosporins.¹ According to a US-based health-record database, cephalosporins accounted for 4% of 269,493 “rash/dermatitis” and 5% of 150,450 “hives/urticaria.”² In Europe and the United States, cefazolin is a frequent cause of perioperative anaphylaxis.³

Diagnosis of cephalosporin hypersensitivity relies on skin tests (STs) with native compounds, followed, when negative, by drug challenges (DCs).

In this issue, Romano et al⁴ report on 236 patients with 249 immediate reactions to cephalosporins. Anaphylaxis was the index reaction in 64.8% of cases. Allergy workup included STs with penicillin reagents and the suspected cephalosporin, serum specific IgE (sIgE) for penicillins and cefaclor (ImmunoCAP; Phadia/Termo Fisher Scientific, Uppsala, Sweden) and, in case of negative results, a DC. A total of 167 patients were positive at the first allergy workup: 162 to STs, 2 had a positive sIgE to cefaclor, and 3 reacted to DCs. Twenty patients, in whom index reactions had occurred >6 months prior, were retested 2 to 4 weeks after a negative DC. This approach revealed a conversion to positive STs in 5 of 6 subjects with anaphylaxis. The time interval between the last reaction and workup was significantly longer in patients with negative STs.

Loss of ST reactivity depends on several variables, including the pathogenic mechanism (IgE vs T-cell mediated), drug or drug class, and patients' pattern of sensitivity. In a 5-year follow-up study of 55 subjects with IgE-mediated penicillin allergy,⁵ STs became negative in approximately 70% of participants; interestingly, loss of ST reactivity was faster in amoxicillin-selective reactors. In another study,⁶ 49 patients with a T-cell-

mediated hypersensitivity to penicillins, who were retested from 1 year to more than 10 years after the first evaluation, continued to have positive patch tests and/or delayed intradermal tests. In a previous report, Romano et al showed that in IgE-mediated cephalosporin allergy, negative STs were more frequent in patients positive only to cephalosporins than in those positive to both penicillins and cephalosporins. Moreover, STs performed after several months can overlook cross-reactivity and give responses falsely selective to the culprit cephalosporins.⁷ The present study endorses these findings and supports the recommendation for an ideal upper time limit of 6 months from the (last) index reaction for STs in patients with immediate reactions to β -lactams, including cephalosporins.⁸ On the other hand, it is advised to use a lower time limit of 3 to 6 weeks for STs in such patients.^{8,9} However, there are clinical scenarios in which the diagnosis is urgently required. In this respect, the question arises whether earlier testing would influence ST sensitivity. Hence, we analyzed data regarding patients with suspected perioperative hypersensitivity who had been tested early (within 6 weeks) and at recommended timing (between 6 weeks and 6 months). For cefazolin, a positive ST was found in 10 of 22 (45.5%) and 37 of 85 (43.5%) of the patients from the early and recommended timing group, respectively. Negative STs were followed by uncomplicated DC in 11 of 12 early tested patients. Half of the 48 patients tested at recommended timing had a negative DC, except one. Clearly, STs for cefazolin have a high negative predictive value, even when performed within 6 weeks after the reaction (unpublished data).

Romano et al⁴ warn that in IgE-mediated cephalosporin allergy, loss of ST reactivity is not per se accompanied by loss of (risk of) clinical reactivity. After a negative DC, a conversion to positive STs may happen when patients are retested within an appropriate time frame. The approximately 3% “resensitization” rate in this study is consistent with other literature.⁸

Another critical issue is to ascertain the best balance of sensitivity and specificity of STs by establishing maximum nonirritating concentrations (NICs). For cephalosporins, recommended NICs diverge but many adopt a maximum NIC of 2 mg/mL.³ However, so far, in most studies, NICs have mainly been established in (unexposed) controls. In clinical practice, one will rather need to study cross-reactivity in patients with a documented allergy to other β -lactams in whom safety of the alternative drugs is finally established by DCs. Using this approach, we showed that for cefazolin, ceftazidime, and aztreonam, the NIC for immediate readings of STs is 20 mg/mL.¹⁰ Here, Romano et al, since 2013, have increased the NIC to 20 mg/mL for all cephalosporins except cefepime.

Methodology (injected volume and device, site, reading time) and criteria for positivity for STs vary between studies.^{8,9} A recent multicenter study showed how critical detailed

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methodological recommendations are for reproducible and comparable results.¹¹ Altogether these results could benefit harmonization between protocols.^{8,9}

At present, identical NICs are recommended for both immediate and delayed ST readings. However, this approach is not substantiated. We have shown that for ceftazidime and aztreonam, the NIC for delayed reading STs can be set at 200 mg/mL.¹⁰ Whether other NICs apply in immediate and non-immediate reactions is an interesting area of research.

Another issue is the absence of reliable *in vitro/ex vivo* tests. The only commercially available *in vitro* test for immediate reactions to cephalosporins is the sIgE assay for cefaclor. However, the reactivity patterns to cephalosporin allergy advocates the need for other assays. Recently, we demonstrated that a ratio of sIgE cefazolin/total IgE $\geq 1.42 \times 10^{-3}$ yielded a sensitivity of 49% and a specificity of 94%.¹² As in penicillin allergy,⁸ loss of sensitization using sIgE was faster than with STs.

Data on CD63- and CD203c-based basophil activation tests (BATs) are scarce. Compound-specific studies with individual dose-finding experiments and calculation of decision thresholds are mandatory for determining the position of the BAT in the diagnostic algorithm.¹³ Note that, as in penicillin allergy, BAT might become negative earlier than sIgE.⁸

The high rate of positive STs in the present study relates to the high percentage of patients with anaphylaxis. Paralleling the observations by others,¹⁴ the rate of ST positivity drops in nonanaphylactic immediate reactions (ie, cutaneous manifestations) fueling the proposal for direct DC in such cases. However, opinions about the significance of urticaria in individual risk assessment currently diverge and need verification. A direct DC as a general rule for urticaria as index reaction might cause severe harm.

Finally, it is important to establish whether STs with benzylpenicillin reagents and semisynthetic penicillins should be systematically performed or whether a simplified diagnostic protocol, limited to the culprit cephalosporin, can be applied in low/intermediate risk subjects.

In conclusion, future needs include standardized and harmonized STs. In immediate reactions, it is crucial to perform these tests within an upper time limit of 6 months from the index reactions and to retest patients who experienced anaphylaxis more than 6 months before allergy workup. We need to develop reliable *in vitro/ex vivo* tests and evaluate the contribution of chemically modified conjugates in improving their performances. Robust evaluations of the impact of clinical presentation of urticarial eruptions on patients' risk profile are required.

The concept that for diagnosis of immediate reactions "time is of the essence" should be spread outside the allergists' community, in order to optimize antibiotic stewardship.

Optimizing both patients' risk assessment and diagnostic tests will benefit, on an individual level, the choice between a

comprehensive allergy workup and direct DC. It will also facilitate the choice between protocols limited to testing only the suspected cephalosporins versus more extensive ones, including penicillin reagents.

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REFERENCES

1. Torres MJ, Celik GE, Whitaker P, Atanaskovic-Markovic M, Barbaud A, Bircher A, et al. A EAACI drug allergy interest group survey on how European allergy specialists deal with beta-lactam allergy. *Allergy* 2019;74:1052-62.
2. Wong A, Seger DL, Lai KH, Goss FR, Blumenthal KG, Zhou L. Drug hypersensitivity reactions documented in electronic health records within a large health system. *J Allergy Clin Immunol Pract* 2019;7:1253-1260.e3.
3. Khan DA, Banerji A, Bernstein JA, Bilgicir B, Blumenthal K, Castells M, et al. Cephalosporin allergy: current understanding and future challenges. *J Allergy Clin Immunol Pract* 2019;7:2105-14.
4. Romano A, Valluzzi RL, Caruso C, Zaffiro A, Quarantino D, Gaeta F. Evaluating immediate reactions to cephalosporins: time is of the essence. *J Allergy Clin Immunol Pract* 2021;9:1648-57.
5. Blanca M, Torres MJ, Garcia JJ, Romano A, Mayorga C, de Ramon E, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol* 1999;103:918-24.
6. Romano A, Viola M, Bousquet PJ, Gaeta F, Valluzzi R, Caruso C, et al. A comparison of the performance of two penicillin reagent kits in the diagnosis of beta-lactam hypersensitivity. *Allergy* 2007;62:53-8.
7. Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quarantino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy* 2014;69:806-9.
8. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams—an EAACI position paper. *Allergy* 2020;75:1300-15.
9. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract* 2020;8:S16-116.
10. van der Poorten MM, Van Gasse AL, Hagendorens MM, Faber MA, De Puyseleir L, Elst J, et al. Nonirritating skin test concentrations for ceftazidime and aztreonam in patients with a documented beta-lactam allergy. *J Allergy Clin Immunol Pract* 2021;9:585-588.e1.
11. Barbaud A, Weinborn M, Garvey LH, Testi S, Kvedariene V, Bavbek S, et al. Intradermal tests with drugs: an approach to standardization. *Front Med (Lausanne)* 2020;7:156.
12. Van Gasse AL, Sabato V, Degerbeck F, DeWitt AM, Oulkadi R, Faber MA, et al. Specific IgE to cefazolin: Does it benefit diagnosis? *J Allergy Clin Immunol Pract* 2019;7:2932-4.
13. Ebo DG, Bridts CH, Mertens CH, Sabato V. Principles, potential, and limitations of ex vivo basophil activation by flow cytometry in allergology: a narrative review. *J Allergy Clin Immunol* 2021;147:1143-53.
14. Touati N, Cardoso B, Delpuech M, Bazire R, El Kara N, Ouali D, et al. Cephalosporin hypersensitivity: descriptive analysis, cross-reactivity and risk factors [published online ahead of print December 29, 2020]. *J Allergy Clin Immunol Pract*. <https://doi.org/10.1016/j.jaip.2020.11.063>.