

Diagnosing Cefazolin Hypersensitivity: Important Steps Forward, but We Haven't Reached the Goal Yet



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Cefazolin is an antibiotic used for a number of bacterial infections. It is on the World Health Organization's List of Essential Medicines, which summarizes the essential medications of a basic health system. Although cefazolin is considered safe, it is known to commonly cause diarrhea, stomach pain, vomiting, and rash. The latter is frequently taken as an indicator of hypersensitivity that must be proven or ruled out because of the potential cross-reaction of cefazolin with other cephalosporins and all β -lactams. And because cefazolin is recommended as an appropriate alternative in patients who are allergic to penicillin,¹ drug hypersensitivity reactions (DHRs) to this first-generation cephalosporin are reported to be an important cause of perioperative anaphylaxis, with serious consequences in the event of diagnostic error.²

The problem starts here: what is the optimal test method to confirm cefazolin hypersensitivity? Because provocation tests with this intravenous cephalosporin are hazardous and cefazolin-specific IgE assays are still missing, the diagnosis of an immediate hypersensitivity to cefazolin currently relies on skin tests. A 2 mg/mL solution is recommended for skin prick and intradermal testing and 5% for patch tests,³ but, according to some publications, concentrations of 20 mg/mL are probably also not irritative and might improve sensitivity without affecting specificity.⁴ And indeed, Uyttebroek and international partners could demonstrate in the current issue of the journal that increasing skin test concentration from 2 mg/mL to 20 mg/mL identified an additional 7 of 19 (27%) patients, who would otherwise have displayed negative skin testing.⁵ Nevertheless, we need a more accurate and potentially less dangerous approach.

Recently the basophil activation test (BAT) was introduced in the diagnostic workup of immediate drug hypersensitivity reactions. The test is based on flow cytometry, with different strategies to identify basophils (anti-IgE, CCR3, CRTH2, and CD203c) and measure their activation (CD63 and CD203c) after stimulation with the culprit drug or its metabolites.⁶ Clinical studies (summarized in reference 6) have yielded

sensitivity values of 22%-55% for penicillin, 64%-86% for neuromuscular blocking agents (NMBAs), 36%-71% for pyrazolones, and 46%-62% for radiocontrast media (RCMs). Specificity ranged from 79% to 96% for penicillins, and up to 100% for NMBAs, pyrazolones, and RCMs. Despite these affirmative results, a few limitations are worthy of mention. The results concerning RCMs do not correlate with the severity of symptoms.⁷ Even more important, BAT protocols are not standardized among the various laboratories in terms of markers, procedures, and drug concentrations.⁶ And labs that perform the BAT for this purpose are scarce. This explains the precautionary clinical recommendation regarding *in vitro* testing for drug hypersensitivity in the ENDA/EAACI Drug Allergy Interest Group position paper: in life-threatening reactions or in high-risk patients, BAT, when available, should be performed before *in vivo* tests including skin tests.⁶

Also in this issue of the journal, Uyttebroek and her lab co-workers⁸ investigated BAT techniques in 18 patients with perioperative anaphylaxis after an intravenous injection of cefazolin and with a positive skin test for the drug. By applying BAT with dual labeling of CD63 and CD203c, the IL-3-free CD63-BAT attained a sensitivity of 38% and a specificity of 94%, whereas the CD203c read-out yielded a sensitivity of 75% and a specificity of 94%, or, when taking into account the 2 nonresponders, a sensitivity of 67%. The authors point out that BAT is the sole *in vitro* diagnostic method available for testing immediate drug hypersensitivity reactions to cefazolin, and their data are convincing regarding its potential usefulness. However, the approach is quite sophisticated, scarcely available anywhere else, and it might not be reproducible at other laboratories. Their experience does confirm the conclusions of experts in the use of this technique that, unlike CD203c, the appearance of CD63 is not a sensitive marker for diagnostic use.⁸ Indeed, a sensitivity of 38% with CD63 is unsatisfactory, but a corrected sensitivity of 67% with both CD63 and CD203c, including the 2 nonresponders, is also not overwhelming. And even more important: what about patients with divergent results in these 2 BAT approaches? Is the positive CD203 test the correct one in patients who test negative on the CD63 test with a positive history and a positive skin test? We need a neutral discriminator or a gold standard.⁹ Only a controlled provocation test that tells us which of the discrepant test results is the correct one in the individual patient will serve this purpose. Feasible? Difficult, but essential to define optimal test results and, finally, the best test protocol.

The protocol and the message conveyed by Uyttebroek and co-workers are correct.⁸ BAT is currently the sole *in vitro* diagnostic procedure available for the evaluation of reactions to cefazolin. I congratulate them on their ingenious and well-worked approach. The critical BAT studies from the past

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decade have considerably improved the quality of data obtained by this technique.¹⁰ However, the main message of the position paper on *in vitro* tests remains⁶: the diagnosis of DHRs is primarily based on a detailed clinical history and *in vivo* procedures, such as skin testing and drug provocation tests. The position paper concludes: however, expert consensus has not been achieved on the value of *in vitro* methods for the diagnosis of DHR. The report of Uyttbroek and co-workers⁸ is an important step, but it will be necessary to validate the currently available *in vitro* tests in a large series of well-characterized patients with DHR and/or to develop new and better diagnostic tests than those available at the present time.

Since its discovery in 1991¹¹ and the first clinical applications in 1994,¹² BAT has been developed as a diagnostic aid in drug allergy. A position paper by the EAACI provides an overview of the practical and technical details as well as the clinical utility of BAT in the diagnosis and management of allergic diseases in 2015.¹³ And the position paper of the EAACI in 2016 on *in vitro* methods has critically addressed unmet needs and defined the pathway to be broached in the future; these will have to be addressed and resolved in due course.⁶ It is interesting that the BAT authors have also demonstrated⁵ a more sensitive skin test concentration for cefazolin and express the opinion that cefazolin hypersensitivity seems to be a selective allergy with good tolerance to other β -lactam antibiotics. Unfortunately, they have not applied BAT in their skin test study to further evaluate this remarkable observation. In addition, as the authors state, the main limitation of their skin test study is that they did not challenge the majority of patients displaying a negative 20 mg/mL intradermal test.⁵

Currently, it seems easier to highlight the problems of *in vivo* and *in vitro* tests in drug allergy than suggest solutions.¹⁴ Uyttbroek and her colleagues, national and international, have taken important steps forward towards finding solutions.^{5,8} But we have clearly not reached the goal yet.

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