

Cephalexin, Cefaclor, and Ampicillin: Points in the Picture of β -Lactam Cross-Reactivity



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Pointillism is a painting technique in which the artist applies small strokes or dots of pure color so that from a distance, the blending of these dots form the full work of art. Famous artists who employed this technique include George Seurat, Paul Signac, and Vincent Van Gogh. In the pointillism technique, without the individual dots of pure color, there would be no full work of art. Conversely, if there is no vision for the final painting, there is no structure for the individual dots of color. I offer a parallel between pointillism and the state of the data regarding β -lactam cross-reactivity. Historically, we have only had some smaller points of data. Macy and colleagues¹ offer us a glimpse into the bigger picture in their article in this issue of *The Journal of Allergy and Clinical Immunology: In Practice*. For the final work of β -lactam cross-reactivity, we need more big picture data and individual points of color to understand how best to proceed with potential cross-reacting drugs in patients reporting β -lactam allergy.

In their study, "Population-based incidence of new ampicillin, cephalexin, cefaclor, and sulfonamide antibiotic 'allergies' in exposed individuals with and without preexisting ampicillin, cephalexin, or cefaclor 'allergies,'"¹ Macy and colleagues performed a retrospective review over a 2-year period of 9 million Kaiser Permanente California patients receiving antibiotic courses. The group has published other analyses based on this cohort, but the current work includes 1,800,663 courses of ampicillin, cephalexin, cefaclor, and trimethoprim-sulfamethoxazole used by 1,235,847 unique individuals.¹ The authors chose to look at ampicillin, cephalexin, and cefaclor (ACC) based on concern regarding side chain cross-reactivity,² and sulfamethoxazole served as a control. The authors looked at new allergies among the target drugs occurring within 30 days of ACC initiation. Allergy was defined broadly for this population-based analysis. The largest conclusion drawn by the authors is that having any drug allergy is a risk factor for developing subsequent allergies. Interestingly, the authors found no significant difference in patients with ACC allergy or sulfa allergy developing a new allergy when they received courses of ACC.¹ Furthermore, they

demonstrated that patients with an existing ACC allergy had a significantly increased rate of sulfamethoxazole allergy compared with those without an existing ACC allergy.¹ The authors conclude that if there were true cross-reactivity between ACC, there should be an increased rate of ACC allergy compared with the control sulfa group, and that new ACC allergy does not occur in a side chain—restricted fashion.¹

Macy and colleagues¹ provide a vision for the part of the final picture of β -lactam cross-reactivity, specifically with ACC. However, more points of color (eg, granular data) are needed before concern about cephalosporin cross-reactivity can be eliminated. In general, with drug allergy, the vast majority of people with allergy labels will be the same color and will tolerate cross-reacting medications or reintroduction of medications to which they are allergic, particularly given the small number of patients with true hypersensitivity among all patients carrying a drug allergy label. However, some patients will be red dots of true hypersensitivity in the picture of cross-reactivity. Macy et al have missed these patients in their analysis. The authors offer that medication decisions are based on the data contained in the electronic health record (EHR), but it is highly likely that many ordering medical providers avoided further use of ACC in the cohort of patients with existing ACC allergy. Therefore, it is possible that patients with the most concerning reaction histories continued to avoid ACC, and we are missing cross-reactivity data in the group of patients with higher risk reaction histories. In a large series of cephalosporin allergy labels, Stone et al³ included 242 patients with both a cephalosporin and penicillin allergy, and 88 patients with a cephalosporin allergy. For immediate reactors, they found that eight patients with a cephalexin allergy had positive skin testing to ampicillin, and three delayed reactors had a positive skin test to ampicillin. Because the work by Stone et al includes two prominent drug allergy referral centers, it undoubtedly includes higher-risk patients, as illustrated by the baseline demographics in this group.³ Regarding the discrepancy between the big picture data of Macy et al, which suggest negligible ACC cross-reactivity, and the data points of Stone et al, which suggest ACC cross-reactivity in a select population, the main conclusion to draw is that risk stratification approaches are needed for ACC use in patients with existing ACC allergy labels. These approaches would help to avoid unnecessary cephalosporin avoidance in most patients and the risks associated with this avoidance, but also to avoid hypersensitivity reactions in the minority of patients truly at risk.

Another finding reproduced in the work of Macy et al¹ and previously shown by others⁴⁻⁶ is that having any drug allergy label and female sex were associated with developing a new drug allergy label. Taking a critical look at these specific patient groups may help flesh out the β -lactam cross-reactivity picture. There is likely a multifactorial explanation for these findings, including

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Conflicts of interest: A. Ramsey is a speaker for GlaxoSmithKline and Sanofi/Regeneron, outside of this publication.

Received for publication December 2, 2021; accepted for publication December 2, 2021.

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J Allergy Clin Immunol Pract 2022;10:556-7.
2213-2198

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<https://doi.org/10.1016/j.jaip.2021.12.004>

genetic predisposition to hypersensitivity reactions, along with psychosocial factors. In an analysis of 592 US Drug Allergy Registry patients, most drug allergy labels were to penicillins (78%) and cephalosporins (12%), and sulfonamides (12%).⁷ Similar to the findings of Macy et al,¹ these more granular data demonstrated that drug allergy concerns increased as the number of reactions increased, and with poor general and mental health.⁷ Female sex was associated with a higher severe allergic reaction concern.⁷ The agreement in findings between these two types of studies (one big picture and one prospective data points) can provide a focus for future research and suggests that revisiting the labels in these particular groups of patients could have the most impact on appropriate antibiotic prescribing.

The current state of EHR data is also an unfortunate artist in the picture of β -lactam cross-reactivity. Although the work of Macy et al¹ work did not delineate historical reaction information (eg, intolerance was not separated from hypersensitivity), they rightfully point out that antibiotic prescribing is dictated by the information contained in the EHR. The suboptimal state of the EHR has been well-documented,⁸⁻¹² including inaccurate and incomplete data, entered by members of the medical team with widely varying levels of training, but usually lacking drug allergy expertise.¹¹ Macy et al fill a void in β -lactam cross-reactivity population data, but improvement in EHR documentation would be hugely beneficial for completing the picture. The EHR limitations are well-recognized in our specialty, and a formal work group from the American Academy of Allergy, Asthma and Immunology Adverse Reaction to Drugs, Biologics, and Latex group is working on a publication with guidance regarding this for 2022 (Guyer A. Personal communication, 2021).

Macy et al¹ have provided important population-based data showing the lack of increased risk for new ACC allergy labels in patients with existing ACC labels. They demonstrate that there is no difference in new ACC allergy labels and sulfamethoxazole allergy labels in those with existing ACC allergy labels. Their work supports that female sex and existing drug allergy labels are a risk for future drug allergy labels. More granular data points, focus on specific populations, and improvement in EHR will

help to add more specific points to the large picture of β -lactam cross-reactivity. Future studies will optimally create a masterpiece of β -lactam cross-reactivity to optimize antibiotic choices for patients.

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