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Non-invasive delabeling and refining of beta-lactam allergy labels in inpatients to optimize antimicrobial stewardship

To the Editor,

Beta-lactam antibiotic allergy labels (AAL) are prevalent, often incorrect, complicate treatment choices, are associated with negative patient outcomes, and drive antimicrobial resistance.^{1,2} Allergy workups are able to invalidate the majority of these AAL but are time-consuming and require invasive skin and provocation testing.^{1,3,4} Therefore, non-invasive delabeling protocols were recently evaluated and shown to be safe and effective in Australia and New Zealand (Table S1). However, inpatient AAL prevalence varies considerably, that is, 10%–20% in US or Australian studies and 5%–7% in European studies.⁵ Limited studies have evaluated the impact of AAL delabeling in an European context, and it remains unknown whether similar non-invasive protocols can be implemented in a European context.

Therefore, we conducted a prospective study enrolling adult inpatients with a beta-lactam AAL. A 3-step methodology was followed: (1) an allergy-focused clinical history was taken using a structured questionnaire; (2) the electronic patient record (EPR) was checked for re-exposure to the culprit or related antibiotics; and (3) the primary physician and community pharmacist were contacted to identify uneventful re-exposure and discordances. Based on these findings, allergy labels were divided into three groups: correct, undetermined, and incorrect labels. A correct AAL was assigned when an allergic reaction was observed in the hospital or when positive skin or provocation testing was found. An undetermined AAL was assigned when there was no proof of (in)correctness of the AAL. An incorrect AAL was assigned when patients reported a non-allergic adverse drug reaction (ADR), when both negative skin and provocation testing were identified, or when uneventful re-exposure to the culprit antibiotic occurred. Within the first two groups, the number of labels that could be refined due to exposure to non-culprit beta-lactams after the index event(s) was assessed. Furthermore, the predictive value of the questionnaire responses was evaluated. Detailed methodology is provided in the Appendix S1.

During a 10-month period, 197 patients were included, with a total of 216 beta-lactam AAL of which 38% (82/216) could be delabeled (Figure 1A, Tables S2–S3). Only 6.5% (14/216) of AAL were considered correct and 56% (120/216) of AAL were considered undetermined. The most frequent reasons for delabeling were uneventful re-exposure to the culprit antibiotic (99%, 81/82), and non-allergic ADRs erroneously attributed to allergy (21%, 17/82) (Figure 1B). Re-exposure was most often detected by reviewing the

EPR (84%, 68/81) followed by confirmation of re-exposure by the community pharmacist (37%, 30/81) (Figure 1C). Based on information of the general practitioner and community pharmacist alone, 13 AAL could be delabeled, representing 16% (13/82) of total invalidated AAL. Refinement was possible for 27% (58/216) of AAL, due to re-exposure to a beta-lactam antibiotic, different than the culprit one (97%, 56/58). Specific beta-lactam antibiotics could be indicated as safe alternatives for the supposed beta-lactam allergy, bypassing the need for the currently recommended supervised rechallenges⁶ (Table S4). For 2 AAL, non-culprit beta-lactams were identified as safe alternatives in an allergy workup. We were not able to identify independent determinants in our questionnaire that were able to predict the outcome, that is, delabeling or not (Table S5). However, the questionnaire provides a guide for non-allergy specialists to tackle AAL and empowers hospitalized patients to improve their medical record themselves.

Our work underscores the pivotal role of a thorough EPR search. Furthermore, it demonstrates the relevance of contacting the patients' primary care physician and pharmacist, which has not yet been systematically studied. We introduce refinement of AAL based on exposure to non-culprit beta-lactam antibiotics and existing data on cross-allergies.^{6,7} This bypasses the need for a test dose or graded challenge after risk assessment,³ as currently recommended, and provides a novel asset that can positively impact antibiotic stewardship.

We showed that a large proportion of AAL were incorrect and could immediately be delabeled. Moreover, an important fraction resulted from erroneously labeling of non-allergic ADRs as AAL, indicating the need for improved teaching of primary care physicians but also other non-allergists on how to correctly document ADRs.

In conclusion, our single-center prospective study shows that a structured strictly non-invasive delabeling protocol can invalidate almost 40% of beta-lactam AAL and refine another 27%. Our study is the first in Europe, in a low prevalent beta-lactam AAL setting, and demonstrates the significance of a thorough EPR review and the added value of systematically contacting primary care healthcare workers. Therefore, we vouch for the (re-)appreciation of the non-invasive allergy evaluation. By implementing this often forgotten yet simple step in clinical practice, many patients that are deemed allergic can be treated with first-line or second-line beta-lactam antibiotics instead of possibly less effective or more toxic alternatives, contributing to antimicrobial stewardship. Automated clinical decision support systems, screening for potential re-exposure to

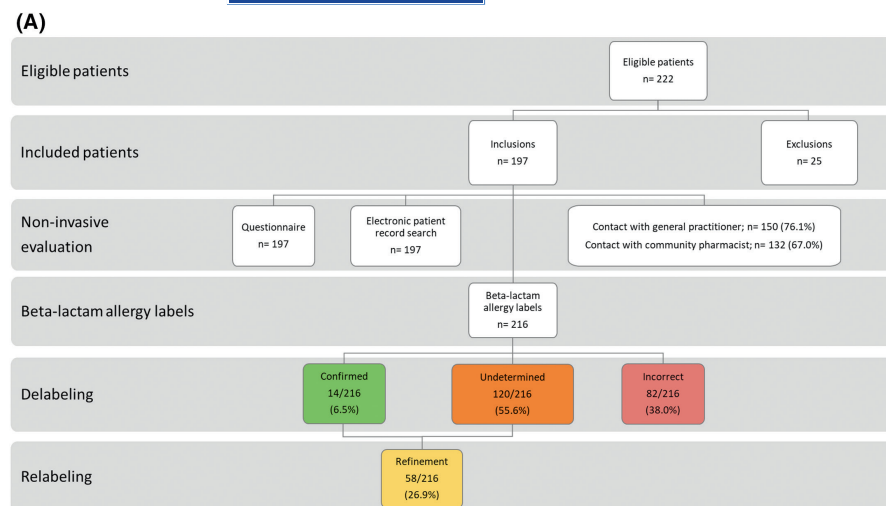
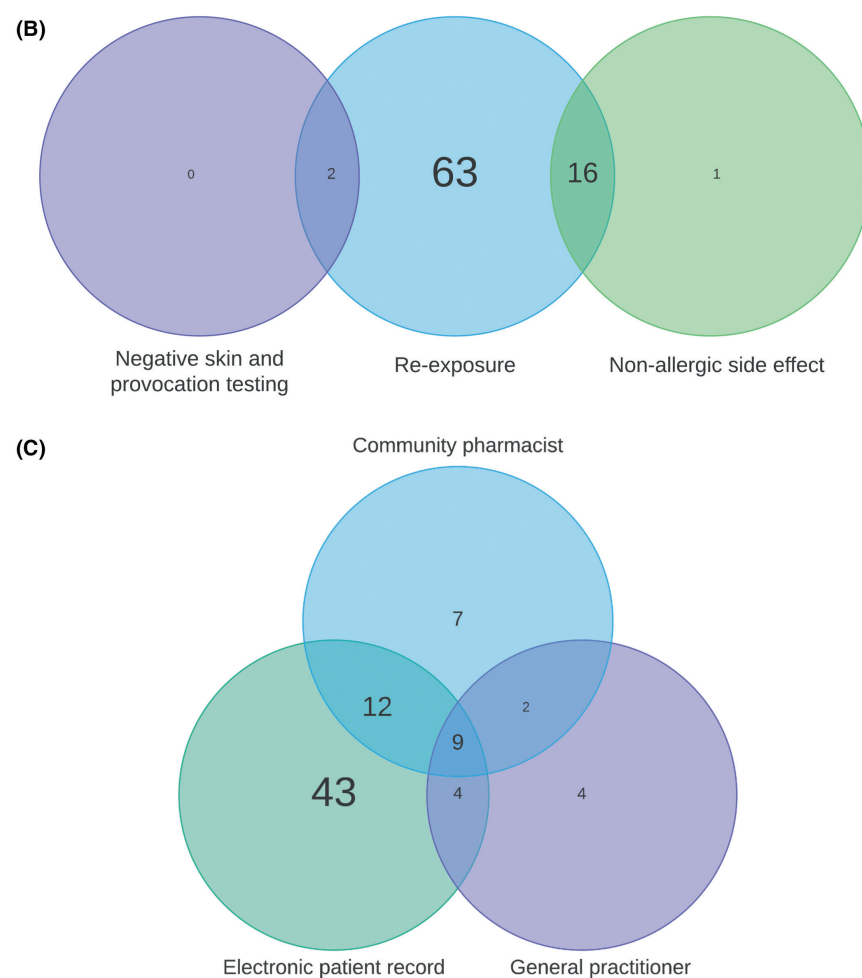


FIGURE 1 Panel A: Study flow diagram and main results. Panel B: Reasons for non-invasive beta-lactam allergy delabeling. Panel C: Information source of re-exposure



the culprit drug, identifying discordances in the medical file and alerting the treating physician, can further improve this approach and should be assessed in future research.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest related to this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Fel d 1 surface expression on plant-made eBioparticles combines potent immune activation and hypoallergenicity

To the Editor,

Allergen immunotherapy (AIT) still remains the only disease-modifying treatment for immunoglobulin E (IgE)-mediated allergies with proven sustained efficacy upon discontinuation of the treatment, provided it is administered regularly for at least 3 years.

Aluminum salts still remain a common depot and adjuvant for subcutaneous AIT that moderately reduce allergenicity; however, the risk of severe allergic reactions persists, making careful up dosing protocols necessary.¹ These characteristics justify the need for shorter treatments with improved safety profiles.

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