

ORIGINAL ARTICLE

Challenging the norm: are cefixime challenges relevant in confirmed penicillin-allergic patients?

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Summary

Background. Growing evidence suggests that cross-reactivity between penicillins and cephalosporins is mainly driven by R1 side-chain similarity rather than the beta-lactam core. Although cefuroxime, ceftriaxone and cefixime appear to have a low cross-reactivity risk, their use in patients with confirmed penicillin hypersensitivity (HS) remains inconsistent. We aimed to assess the prevalence of HS to cephalosporins with structurally distinct R1 side chains in patients with penicillin allergy. **Methods.** A retrospective analysis of patients who completed allergy workup between 2010 and 2024 at a tertiary center was conducted. Patients with confirmed penicillin HS – established by positive specific IgE, basophil activation test, lymphocyte transformation test, positive skin tests (ST), positive drug provocation tests (DPT), and/or reproducible severe reactions – were included. Patients underwent ceftriaxone ST and cefixime or cefuroxime DPT to assess tolerance to an alternative beta-lactam. **Results.** Among 241 patients with confirmed penicillin HS, 214 (88.8%) underwent alternative DPT with cefixime (n =

210) or cefuroxime (n = 4). One patient (0.4%) had a positive intradermal ST to ceftriaxone and was not challenged with the alternative cephalosporin. Two patients (0.9%) developed HS reactions during cefixime DPT. Overall, 98.8% of patients tolerated the selected cephalosporins (95% CI 96.3-99.7). A pediatric subgroup was included (n = 40, 16.6%), and no child reacted to the alternative cephalosporins. **Conclusions.** In this 14-year real-life cohort, 98.8% of the patients with confirmed penicillin HS tolerated a cephalosporin with a structurally distinct R1 side chain, supporting its' safe use in those cases and suggesting that routine hospital-based alternative DPT may be unnecessary in selected patients.

KEY WORDS

Antibiotic resistance; penicillins; cephalosporins; beta-lactam cross-reactivity; R1 chain.

IMPACT STATEMENT

Demonstrating 98.8% tolerance in penicillin-allergic patients, this hospital-based study supports safe use of cefuroxime, ceftriaxone or cefixime use, optimizing antibiotic stewardship and resource utilization while providing clinically relevant and translatable evidence.

Introduction

Beta-lactam (BL) antibiotics remain the mainstay of therapy for a broad range of bacterial infections because of their efficacy and favorable safety profile (1,2). However, BLs—particularly penicillins—are the most common cause of drug-induced hypersensitivity (HS) reactions and continue to pose a major challenge in clinical practice (3–6).

Accurate identification of true BL allergy and careful characterization of the suspected reaction are essential. In the absence of a structured allergy evaluation, patients are frequently labeled as allergic to the entire BL class, leading to unnecessary avoidance (7,8). This results in the use of broader-spectrum or less effective antibiotics, contributing

to suboptimal treatment and the development of antimicrobial resistance which leads to higher healthcare costs (9–11). A clear understanding of BL cross-reactivity is therefore critical to support safe, rational, and evidence-based prescribing in cases of suspected penicillin HS (12,13).

Beta-lactams comprise a heterogeneous group of antibiotics that share a common β -lactam ring, including penicillins, cephalosporins, carbapenems, and monobactams. Their immunologic properties are largely determined by structural differences in their side chains. Penicillins contain 5-membered thiazolidine ring attached to the β -lactam core, with a single R side chain that differentiates individual compound. Cephalosporins have a 6-membered sulfur-containing dihydrothiazine ring and 2 side chains (R1 and R2), which distinguish the different molecules (14). Carbapenems contain a carbon double bond instead of sulfur in the 5-membered thiazolidine ring and have a single R side chain, which distinguishes the different carbapenems. Aztreonam is the only monobactam commercially available and it contains only the β -lactam ring (15).

Recent evidence indicates that cross-reactivity between penicillins and cephalosporins is primarily driven by similarity of the R1 side chain rather than by the shared β -lactam core (16–19). Aminocephalosporins, such as cephalexin, cefadroxil, and cefaclor, that share identical R1 side chains with aminopenicillins are associated with a higher risk of cross-reactivity, reported to be approximately 16.5%. In contrast, the overall risk of cross-reactivity between penicillins and cephalosporins as a class is estimated to be below 2% (20,21). These findings challenge the routine avoidance of all cephalosporins in patients labeled as penicillin allergic.

Similarly, cross-reactivity among cephalosporins is primarily determined by structural similarities in their R1 side chains rather than by their classification into generations, which primarily reflects their antibacterial spectrum. Thus, cephalosporins with similar R1 side chains may cross-react irrespective of their generation. In particular, cefuroxime, and ceftriaxone share a methoxyimino moiety in the R1 side chain and have been

associated with cross-reactivity. Conversely, cefixime has a structurally distinct R1 side chain and should therefore be considered separately when assessing potential cross-reactivity (22,23).

Despite the clinical relevance of this issue, standardized guidelines for the use of alternative BLs in patients with confirmed penicillin HS remain limited, and few systematic reviews have addressed cross-reactivity patterns in this population. Nevertheless, based on the evidence that cross-reactivity is largely determined by R1 side-chain similarity, an increasing number of authors have recently supported the direct use of structurally dissimilar R1 side chains cephalosporins in patients with confirmed HS to penicillins without prior DPT (21,24).

In our department, patients with confirmed HS to penicillins have routinely undergone skin tests (ST) with ceftriaxone, followed—if negative—by a drug provocation test (DPT), typically with cefixime (or, less frequently, with cefuroxime), to ensure the availability of a safe alternative within the BL class and exclude BL core driven HS. In light of the recent evidence indicating that cross-reactivity is primarily driven by similarities in the R1 side chain, the present study aimed to assess whether these findings are replicated in our local population, and to determine whether the risk-benefit balance of routine hospital-based DPT with cefuroxime or cefixime should be reassessed in selected patients with confirmed HS to penicillins.

Methods

Study design and setting

We conducted a retrospective analysis at the Allergy Department of São João University Hospital, a tertiary referral center in Porto, Portugal, by reviewing the medical records of all patients who completed a drug allergy workup between January 2010 and December 2024. Medical records were reviewed between January and December 2025.

Patients with confirmed penicillin HS identified during the study period, regardless of age, were included in the analysis. HS was considered confirmed when:

- In immediate reactions (occurring within one hour after the last drug administration): one of the following criteria was present: positive specific IgE to penicilloyl G and/or V, and/or amoxicillin; positive basophil activation test (BAT); positive skin prick test (SPT) or intradermal test (IDT); positive diagnostic DPT; and/or a documented reproducible severe reaction (anaphylaxis) (25).

- Non immediate reactions (occurring more than one hour after the last drug administration or reactions of unknown timing): one of the following criteria present: positive lymphocyte transformation test (LTT); positive patch test; positive delayed-reading IDT; positive diagnostic DPT; Severe cutaneous adverse reactions (SCARs) were not eligible for inclusion (26).

Clinical data were extracted from medical records, including patient demographics and details of the index reaction—namely the index drug, latency time, and clinical manifestations—as well as documented tolerance and/or reactions to other BL antibiotics. Reactions were classified as immediate or non-immediate based on predefined temporal criteria.

Allergy workup

Skin testing

Skin testing was performed using benzylpenicilloyl–poly-L-lysine (PPL), Minor Determinant (MD) preparation (Diater®, Madrid, Spain), benzylpenicillin, amoxicillin/clavulanic acid and other semisynthetic penicillins, and ceftriaxone, using previously validated as nonirritant concentrations (25).

SPT were performed on the volar surface of the forearm. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. SPT were read at 15 minutes and considered positive when a wheal of at least 3 mm in diameter greater than the negative control, with surrounding erythema, was observed. If negative, IDT were subsequently performed and considered positive when the initial wheal diameter increased by at least 3 mm, accompanied by erythema after 20 minutes. In patients with a history of severe immediate reactions, IDTs were performed using progressively increasing concentrations, starting with a 1/100 dilution, followed by a 1/10 dilution if negative, to minimize the risk of systemic reactions (25).

For the evaluation of non-immediate reactions, patch tests and/or delayed-reading intradermal tests were performed. Patch tests were prepared using crushed commercial tablets (amoxicillin 500mg, amoxicillin/clavulanic acid 1000mg) or the content of intravenous vials (Ceftriaxone 1g; benzylpenicillin 1 million IU, piperacillin/tazobactam 4.5g) diluted to a concentration of 30% in petrolatum, applied to the upper back using Finn Chambers (27). Patch tests were read at 72 hours and were considered positive in the presence of erythema, papules, or vesicles. Delayed IDTs were performed using the same technique as immediate IDT but were considered positive when sustained erythema and induration developed at the injection site within 48 hours (25).

Skin test protocol remained stable over the 14-year study period.

In Vitro Testing

Serum-specific IgE to penicilloyl G and/or V and/or amoxicillin was measured using ImmunoCAP (Thermo Fisher Scientific) when clinically indicated. Results ≥ 0.35 kU/L were considered positive. BAT was performed in selected cases using flow cytometry to measure CD63 and CD203c expression on basophils after stimulation with penicillins as well as ceftriaxone. BAT became accessible at our center in 2023. LTT was performed

in selected cases of non-immediate reaction. Peripheral blood mononuclear cells were cultured in the presence of the suspected antigen, and lymphocyte activation was assessed by measuring DNA synthesis through incorporation of radiolabeled [³H]-thymidine. Proliferative responses were quantified as counts per minute (cpm) and typically expressed as a stimulation index (SI) relative to unstimulated controls. A SI over 3 was considered indicative of sensitization to a specific drug.

Drug provocation testing

In patients with previous negative or inconclusive prior workup, DPT was performed in a controlled hospital setting to confirm or exclude penicillin HS. In patients with confirmed penicillin HS, alternative DPT with cefixime or cefuroxime was performed to assess tolerance to a structurally dissimilar cephalosporin. A stepwise protocol with incremental dosing at 30-minute intervals was used until the full therapeutic dose was reached: 1 g for amoxicillin, amoxicillin and clavulanic acid 875/125mg, 400 mg for cefixime, 250 mg for cefuroxime (examples of provocation test protocols are available in the Supplementary Material; see Table S1). Patients were closely monitored throughout the procedure, and appropriate emergency treatment was immediately available (26). In patients with suspected non-immediate reactions, a 3-day DPT was performed. The hospital-based dose was administered on day 1, followed by a 16-hour washout period and therapeutic doses at home over the following two days (26).

DPT was considered positive if objective signs or symptoms of HS developed during or after the challenge, including:

- For immediate reactions: urticaria, angioedema, bronchospasm, hypotension, anaphylaxis
- For non-immediate reactions: maculopapular exanthema, delayed urticaria, or other delayed manifestations

Patients who developed reactions during DPT were treated according to the type and severity of the reaction with antihistamines, corticosteroids, bronchodilators, and/or epinephrine as needed. All reactions were documented in detail, including time of onset, clinical manifestations, treatment administered, and outcome. Patients were instructed to report any delayed reactions occurring within 24h after discharge, and up to 7 days in case of delayed reactions.

Over the 14-year study period, cefuroxime was recently added as an alternative option for DPT. The choice between cefixime and cefuroxime for alternative DPT was primarily determined by drug availability at our hospital. Another relevant change was the direct performance of DPT with the suspected drug in patients with non-immediate and non-severe index reaction and with a very remote history of penicillin HS, without criteria for a severe immediate reaction (28).

Among patients who had already tolerated a R1 side chain dissimilar cephalosporin after the index reaction, all had previously tolerated at least one of the following: cefuroxime, ceftriaxone, or cefixime. These patients did not undergo an alternative DPT with cefuroxime or cefixime, as an alternative cephalosporin had already been identified. Accordingly, cefuroxime, ceftriaxone, and cefixime were the cephalosporins considered in the present analysis and are hereafter referred to as the alternative cephalosporins. Nevertheless, documented tolerance was considered specific to the tolerated cephalosporin.

Outcomes

The primary outcome was the proportion of patients with confirmed penicillin HS who tolerated cefixime or cefuroxime during DPT (tolerance rate) or, conversely, the proportion who developed HS reactions during alternative DPT.

As secondary outcomes, tolerance rates in pre-specified subgroups were also assessed (immediate vs. delayed reactions, pediatric vs. adult patients, severe vs. non-severe index reactions), as well as the association between ceftriaxone skin test results and tolerance to other cephalosporins, considering R1 side-chain structural similarity and characteristics of patients who reacted to cefixime.

Statistical analysis

Patient demographics, clinical characteristics, and diagnostic outcomes were analyzed descriptively. Continuous variables were summarized as means with standard deviations or as medians with interquartile ranges, as appropriate. Categorical variables were expressed as absolute numbers and percentages. Statistical analyses were performed using SPSS software, version 29 (IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Given its retrospective design and the use of fully anonymized data, formal review and approval by the local institutional ethics committee were not required in accordance with institutional and national regulations. All data were anonymized prior to analysis to ensure patient confidentiality.

Results

Between January 2010 and December 2024, 2,143 patients (362 children) with suspected penicillin HS were evaluated at the Drug Allergy Unit. Penicillin HS was confirmed in 241 patients (11.2%). The diagnostic workup of the included patients is summarized in Figure 1. Among the 241 confirmed cases, 150 (62.2%) were female. The median age was 39.8 years (IQR: 31.65). A pediatric subgroup of 40 patients (16.6%) was included, with a median age of 7.2 years. Demographic and clinical characteristics are reported in Table I.

The most frequently implicated drug was amoxicillin with clavulanic acid in 150 patients (62.2%), followed by amoxicillin in 51 patients (21.1%), penicillin G or V in 35 patients (14.5%), piperacillin/tazobactam in 2 patients (0.8%), ampicillin in 2 patients (0.8%), and flucloxacillin in 1 patient (0.4%) (Table II). The median time from index reaction to allergy workup was 3 years (IQR: 6.25). Comorbidity data were not systematically recorded.

Immediate reactions were identified in 111 patients (46.1%), including 54 (48.6%) with anaphylaxis. In 8 patients (7.2%), the diagnosis was established based on severe reactions (anaphylaxis). Serum-specific IgE to penicillin G, penicillin V, and/or amoxicillin was measured in 108 patients (97.3%), with 26 patients (24.1%) showing positive results for at least one of these specific IgE antibodies. Only one patient underwent a BAT with a positive result for amoxicillin. ST with penicillin major and minor determinants, penicillin, amoxicillin–clavulanic acid, and ceftriaxone was performed in 103 patients (92.8%) and was positive for at least one of them in 54 individuals (52.4%). DPT was conducted in 105 patients (94.6%). Among these, 22 patients (20.7%) underwent diagnostic DPT, all of which yielded positive results. Of these, 21 patients subsequently underwent alternative DPT with cefixime, all were negative; one patient did not undergo cefixime challenge, as they had previously tolerated an alternative cephalosporin. Eighty-three patients (74.7%) underwent alternative DPT with cefixime because the diagnosis of penicillin HS had already been established. Among the 83 alternative DPTs, 82 were negative and 1 was positive. Six patients (5.4%) did not undergo either diagnostic or alternative DPT. Five had previously tolerated an alternative cephalosporin following the index reaction, while one had a positive skin test to penicillin and ceftriaxone and did not undergo alternative DPT. The diagnostic workflow is presented in Figure 2.

Delayed reactions were identified in 119 patients (49.4%), most frequently presenting as maculopapular exanthema without severity criteria (74.7%). LTT was performed in five patients (4.2%), with two patients showing positive results to penicillin and/or amoxicillin.

ST with penicillin major and minor determinants, penicillin, amoxicillin–clavulanic acid, and ceftriaxone were performed in 98 patients (82.4%), with positive results for at least one of them in 45 individuals (45.9%). Overall, DPT was performed in all 119 patients, including 72 diagnostic challenges (60.5%), all of which yielded positive results. Of these, 51 patients subsequently underwent alternative DPT with cefixime and 3 with cefuroxime, all of which were negative. Eighteen patients had already tolerated an alternative cephalosporin following the index reaction and therefore were not submitted to an alternative DPT. Forty-seven patients underwent alternative DPT from the outset. Among these patients, 46 had a negative DPT with cefixime and 1 had a positive one. The workflow is presented in Figure 3.

Eleven patients (4.6%) with confirmed penicillin HS reported reactions of unknown timing, most presenting with maculopapular exanthema without severity criteria (90.9%). Serum-specific IgE was measured in 8 patients (72.7%), of whom 2 (25.0%) had positive results. Nine patients (81.8%) underwent ST with both immediate and delayed readings, with one positive immediate result and two positive delayed results. Six patients underwent diagnostic DPT, all of which were positive. Of these, five patients subsequently underwent alternative DPT; all challenges were negative. Three patients (27.3%) underwent alternative DPT from the outset, all of which were negative. The remaining two patients did not undergo DPT. Both had an established diagnosis of penicillin HS and had already tolerated an alternative cephalosporin. The diagnostic workflow is illustrated in Figure 4.

The pediatric subgroup with confirmed penicillin HS included 40 patients (16.5%), of whom 13 (32.5%) were female, with a median age of 6.7 years (IQR, 8.7). Immediate reactions occurred in 8 patients (20.0%), delayed reactions in 30 (75.0%), and reactions of unknown timing in 2 (5.0%). All pediatric patients tolerated an alternative cephalosporin, and no reactions were observed in this subgroup.

Among patients with an index reaction to amoxicillin–clavulanic acid (n=150, 62.2%), four also reported reactions to other penicillins (penicillin, n=2; amoxicillin, n=2). Among the 146 patients with reactions exclusively to amoxicillin–clavulanic acid, 18 (12.3%) had positive specific IgE for penicillin and/or amoxicillin, 16 (11.0%) had at least one positive ST to penicillin determinants (MD, PPL, or penicillin), and 5 (3.4%) underwent diagnostic DPT with amoxicillin, which was positive. In 107 patients (71.3%), the diagnosis was established as follows: in 43 based on positive skin tests exclusively to amoxicillin–clavulanic acid, in 60 based on a positive DPT with amoxicillin–clavulanic acid, and in 4 on severe reactions.

Overall, 214 patients (88.8%) underwent an alternative DPT with cefixime (n=210) or cefuroxime (n=4), all of whom had previously undergone ceftriaxone skin testing. Of these, 212 patients with negative ceftriaxone SPT and IDT tolerated the cefixime or cefuroxime, whereas two patients, also with negative ceftriaxone skin tests, reacted to cefixime. All four patients who tolerated cefuroxime had previous negative ceftriaxone skin tests. One additional patient (0.4%) had a positive ceftriaxone skin test and did not undergo an alternative DPT.

In addition to the patient with a positive IDT to ceftriaxone, two other patients (0.8%) challenged with cefixime developed HS reactions, as previously described. One patient, with a history of anaphylaxis to amoxicillin–clavulanic acid and positive specific IgE to amoxicillin, developed general malaise, dizziness, pallor, hyperhidrosis, and hypotension. The patient was treated with intravenous antihistamines, corticosteroids, and intramuscular epinephrine, with full recovery. Acute tryptase was 2.92 µg/L. The second patient, with a delayed reaction and a positive intradermal test to amoxicillin–clavulanic acid, developed generalized pruritus and exanthema 2 hours after DPT with

cefixime and was treated with corticosteroids and antihistamines, with clinical improvement. Both patients were advised to avoid penicillins and all cephalosporins.

Overall, during the 14-year study period, tolerance to an alternative cephalosporin could not be established in only three patients (1.2%) with confirmed penicillin HS. Two patients reacted to cefixime during DPT, whereas one had a positive ceftriaxone skin test and did not undergo an alternative DPT.

Discussion and conclusions

This 14-year real-life study demonstrates that HS to selected alternative cephalosporins with R1 side chains distinct from the culprit penicillins is uncommon among patients with confirmed penicillin HS, occurring in only 1.2% of cases (overall tolerance: 98.8%; 95% CI, 96.3–99.7%). These findings support the use of appropriately selected cephalosporins as alternative BL in patients with confirmed penicillin HS.

This low prevalence is consistent with the established concept that cross-reactivity between penicillins and cephalosporins is primarily driven by similarity in the R1 side chain rather than by recognition of the BL core (29,30). Cefuroxime, ceftriaxone and cefixime, possess an R1 side chain that is structurally distinct from those of penicillins, which likely explains the minimal overlap in HS observed in our cohort (31–33). Previous studies have estimated cross-reactivity rates below 2% when side-chain homology is absent, a finding that is closely mirrored by our results (34,35). The concordance between the prevalence observed in our real-life cohort and that reported in prior independent series strengthens the external validity of our findings and supports the clinical reliability of this estimate in routine practice. These findings have important implications for routine hospital practice, where antibiotic selection is often influenced not only by precautionary attitudes among non-specialist physicians but also by electronic alerts that may lead to unnecessarily broad avoidance (36,37).

Nevertheless, a small number of cases in our cohort did not fully align with this pattern and warrant consideration. Despite structural dissimilarity, one of our patients had a positive ST to ceftriaxone and was not challenged. This can be explained by the presence of co-sensitivity to both penicillin and ceftriaxone (38), or by a false positive IDT, with a 5% rate previously shown (23,39). Moreover, we are recently seeing an increasing use of these drugs, which may lead to sensitization that does not necessarily translate into a true allergy, as has been demonstrated for other BL (40–42). Additionally, two patients who reacted to cefixime had negative skin tests to ceftriaxone, highlighting that tolerance to cephalosporins cannot be inferred from skin testing with a structurally distinct cephalosporin (43). These findings reinforce the importance of R1 side-chain similarity when assessing cephalosporin cross-reactivity and selecting alternative agents. Furthermore, although cephalosporin ST is routinely used in clinical practice, its diagnostic performance is less well validated than that of penicillin ST (44,45).

Our data further indicate that the likelihood of reacting to cefuroxime or cefixime did not differ substantially between patients with immediate and delayed penicillin HS, as previously observed in the literature (46). This observation suggests that the underlying immunological mechanism—IgE-mediated or T cell-mediated—does not significantly modify the risk of cross-reactivity when structurally dissimilar BL are used (15).

The clinical relevance of index reaction severity remains uncertain. In our cohort, one of the patients who reacted to cefixime had a history of anaphylaxis to amoxicillin. Although this does not establish severity as a predictor of cross-reactivity, it supports a more cautious approach in patients with severe immediate reactions, as has been recommended. In this subgroup, supervised challenge with structurally dissimilar BL in a hospital setting may be advisable, even in the absence R1 side-chain similarity (24).

Furthermore, the rate of confirmed BL allergy in the paediatric cohort was higher than generally reported (47,48). Viral infections, particularly common in children, may promote

drug-specific T-cell activation by providing co-stimulatory signals for hapten-induced neoantigens and enhancing pharmacological interactions with immune receptors (p-i) (49). Moreover, as a tertiary referral centre, patients are frequently referred from emergency departments or other specialist clinics because of a suggestive clinical history, potentially resulting in a higher pre-test probability of BL HS.

Several limitations should be acknowledged. Its retrospective nature resulted in heterogeneous protocols and reliance on medical record documentation, which may have led to imprecise characterization of the index reactions. It may also have introduced selection bias, as 26 patients did not undergo alternative DPT because they had a reliable diagnostic work-up and had already tolerated another structural dissimilar cephalosporin, resulting in a subgroup with a lower a priori risk of reaction that was not evaluated under the same conditions as the remaining cohort. Additionally, the single-center design may limit the generalizability of our findings. The small number of cross-reactivity events (n=3) precluded multivariable analysis to identify independent predictors.

An important limitation of this study is the absence of an isolated evaluation of clavulanic acid HS. Specific amoxicillin and clavulanic acid preparations for ST were not available at our centre during the study period; therefore, ST was performed using the available intravenous formulation containing amoxicillin and clavulanic acid in combination. Moreover, isolated testing with clavulanic acid was not routinely performed, as it was not widely recognized as a cause of HS reactions (50,51). Notably, in 107 patients (44.4%), the diagnosis was established based solely on positive ST or positive DPT with amoxicillin/clavulanic acid, including patients with severe reactions. However, emerging evidence has since shown that clavulanic acid may account for up to approximately 30% of immediate allergic reactions to amoxicillin/clavulanic acid (52,53). Consequently, the number of patients classified as allergic to aminopenicillins in our cohort may have been

overestimated, as some reactions could instead have been attributable to clavulanic acid. We also did not systematically assess whether patients with negative DPT used cefuroxime/third-generation cephalosporins subsequently or collect data on real-world outcomes after hospital discharge. Finally, we did not perform a cost-effectiveness analysis comparing hospital-based DPT to direct prescription, which would strengthen the resource utilization argument.

Despite these limitations, our study has several strengths, particularly the rigorous diagnostic confirmation of penicillin HS, as only 8 patients (3.3%) were classified based solely on clinical history of severe anaphylactic reactions, without additional confirmatory testing. The study systematically used delayed-reading intradermal testing in non-immediate and unclear reactions, enhancing the detection of T-cell-mediated HS. A major strength is also the inclusion of pediatric patients. Real-life design enhances the clinical applicability of our findings and provides data relevant to routine allergy practice.

In conclusion, our results support the safe use of selected cephalosporins, particularly cefixime, among patients with confirmed penicillin HS. In this 14-year real-life cohort, reactions to cefuroxime, ceftriaxone, or cefixime were uncommon, supporting their role as safe alternative BL. These findings raise the possibility that routine hospital-based cefuroxime or cefixime DPT may be unnecessary in selected patients. However, our data do not establish index reaction severity as a predictor of cefuroxime or cefixime tolerance, greater caution in patients with severe index reactions, such as anaphylaxis, should be regarded as a precaution. Further prospective multicenter studies are needed to identify which patients can safely forgo routine cephalosporin alternative DPT.

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Contributions

AVS and ALP were responsible for formal analysis, methodology, writing—original draft preparation, and writing—review and editing. DBA, JM, AMM, and LA contributed to methodology and writing—review and editing. EDC, JC, and LCL were responsible for conceptualization, methodology, writing—review and editing, and supervision. All authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this article.

Use of Artificial Intelligence: Artificial intelligence tools were used exclusively for language improvement. All scientific content, data interpretation, and final manuscript revision were performed and verified by the authors.

Ethical Approval

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. Given its retrospective design and the use of fully anonymized data, formal review and approval by the local Ethics Committee were not required according to institutional and national regulations.

Informed Consent

Informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

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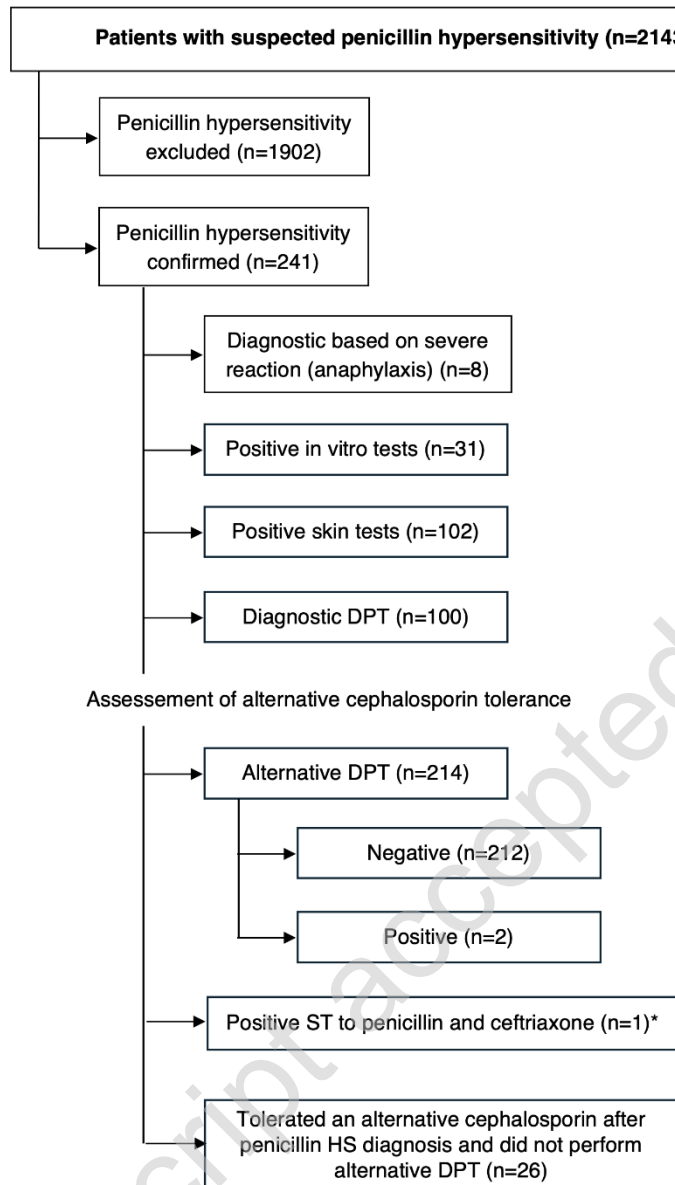
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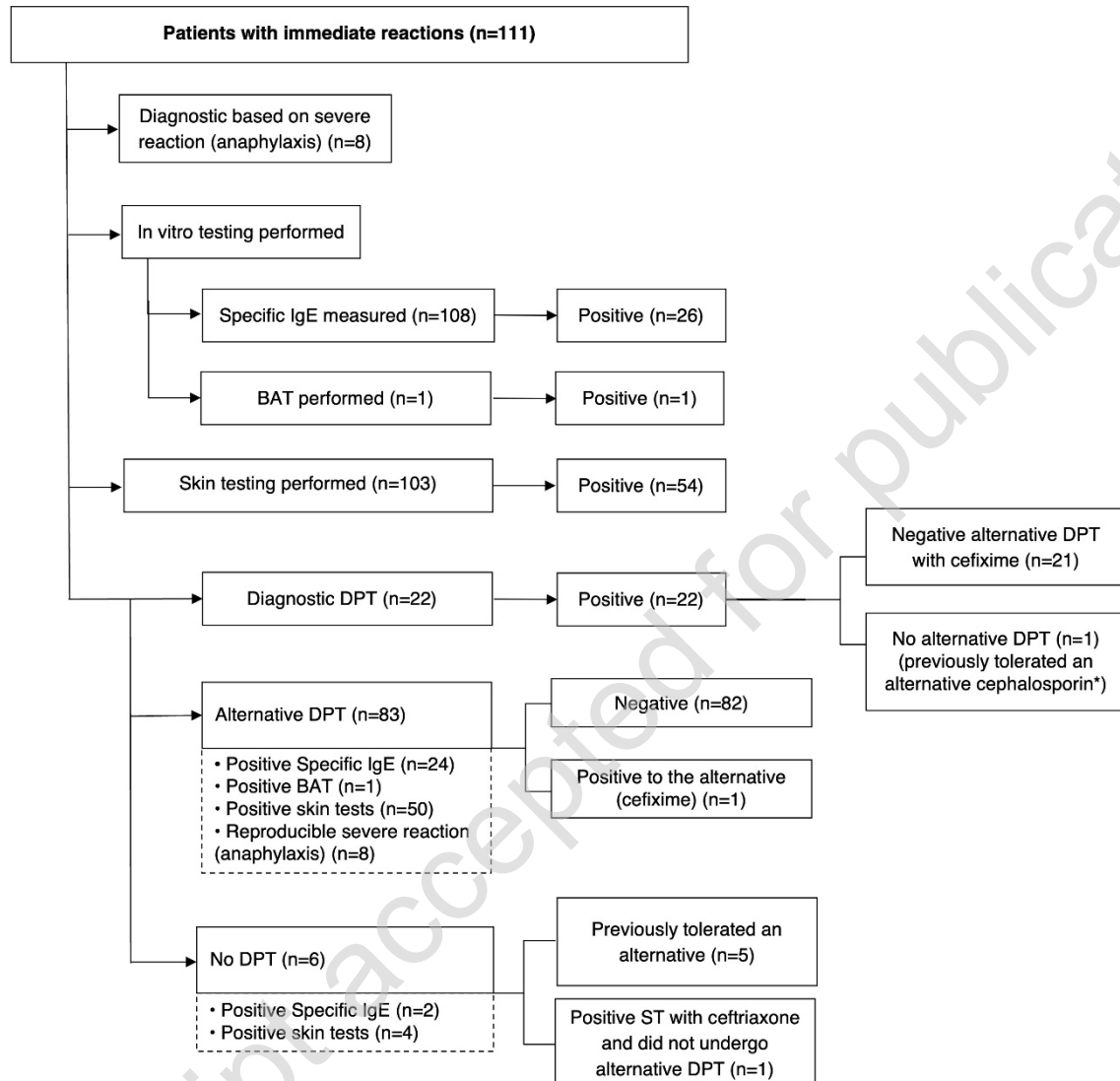
Figure 1. Overall diagnostic workflow and assessment of alternative cephalosporin tolerance in patients with confirmed penicillin hypersensitivity.



Abbreviations: DPT, drug provocation test; HS, hypersensitivity; ST, skin test.

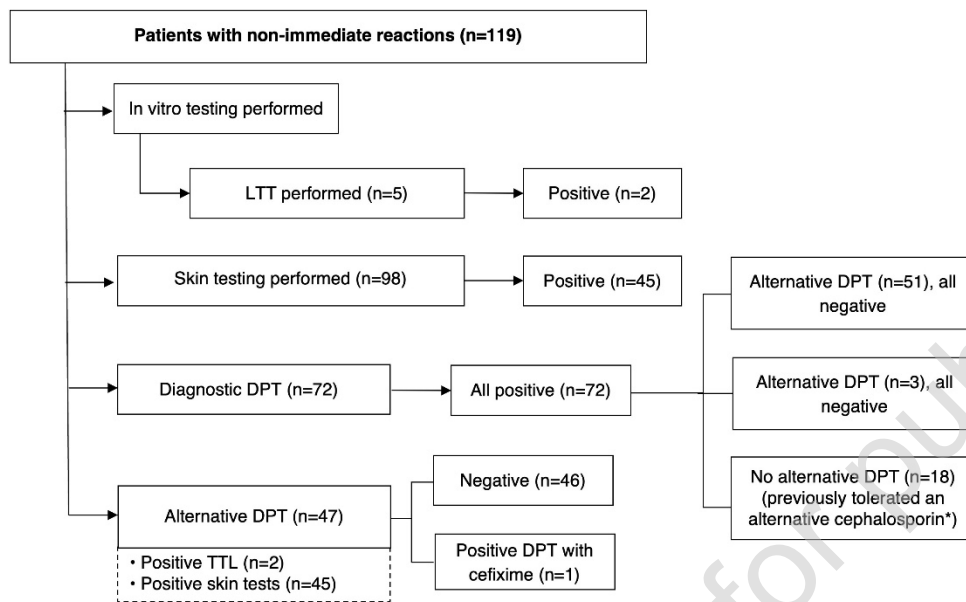
*This patient did not undergo diagnostic or alternative DPT because of positive skin tests to both penicillin and ceftriaxone.

Figure 2. Diagnostic workflow of the allergological workup in patients with immediate reactions to penicillins.



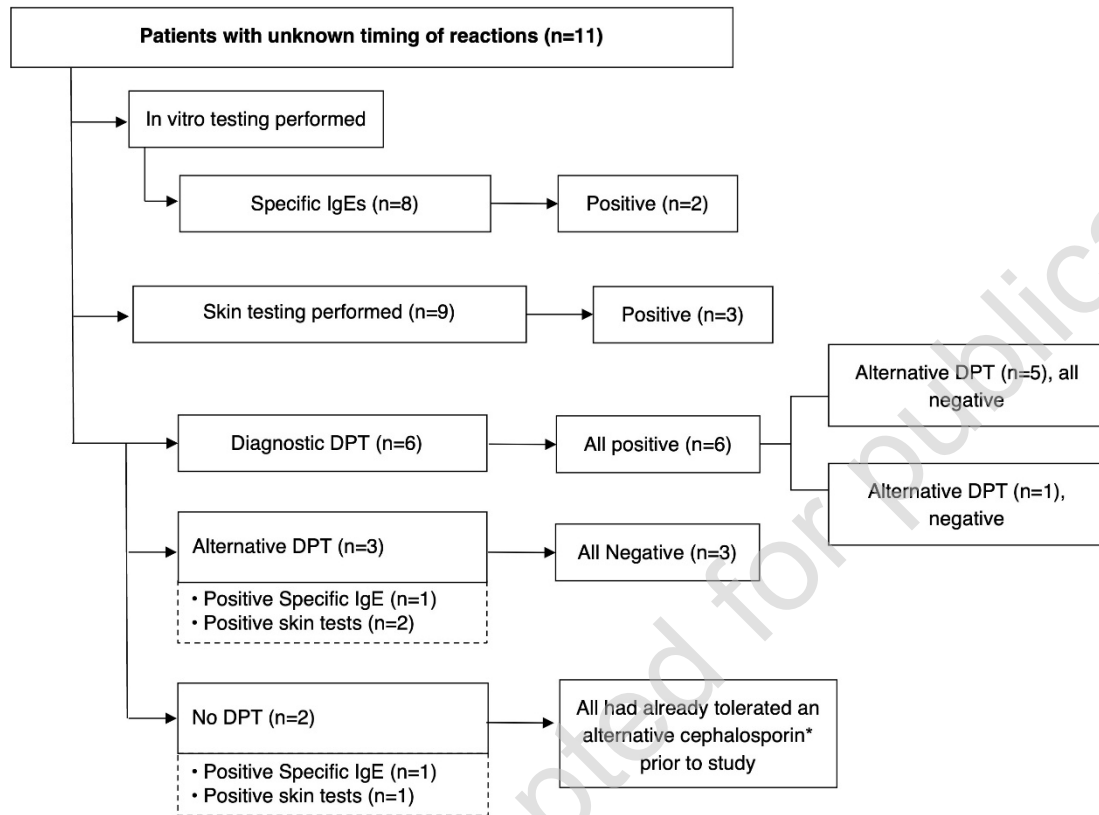
Abbreviations: BAT, basophil activation test; DPT, drug provocation test; HS, hypersensitivity; IgE, immunoglobulin E; ST, skin test.
 *Alternative cephalosporin" as at least one of the following: cefuroxime, ceftriaxone or cefixime.

Figure 3. Diagnostic workflow of the allergology workup in patients with non-immediate reactions to penicillins.



Abbreviations: DPT, drug provocation test; HS, hypersensitivity; LTT, lymphocyte transformation test.
 *Alternative cephalosporin" as at least one of the following: cefuroxime, ceftriaxone or cefixime.

Figure 4. Diagnostic workflow of the allergology workup in patients with unknown timing of reactions to penicillins.



Abbreviations: DPT, drug provocation test; HS, hypersensitivity; IgE, immunoglobulin E.
 Alternative cephalosporin as at least one of the following: cefuroxime, ceftriaxone or cefixime.

Table I. Demographic characteristics of the sample (n = 241)

Variable	Value
Age, yo, median (IQR)	39.8 (31-65)
Gender	
Female	150 (62.2)
Male	91 (37.7)
Children (<18yo)	40 (16.6)

Data are presented as n (%) unless otherwise indicated. IQR, interquartile range.

Table II. Beta-lactam antibiotics implicated in the hypersensitivity reactions.

Responsible beta-lactam	n (%)
Penicillin G or V	35 (14.5)
Amoxicilin/clavulanic acid	150 (62.2)
Amoxicilin	51 (21.1)
Piperacillin/Tazobactam	2 (0.8)
Ampicillin	2 (0.8)
Flucloxacillin	1 (0.4)