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Penicillin allergy management strategies relevant for clinical practice - a narrative review

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Running head: Penicillin allergy management strategies

Abstract: Penicillin allergy is the most commonly reported drug allergy, with prevalence rates ranging from 6% to 31% across various populations and geographic areas. The penicillin allergy label is linked to higher mortality and morbidity rates, extended hospital stays, increased readmission rates, and a greater reliance on second-line antibiotics. Research indicates that nearly 99% of those labeled as penicillin-allergic can tolerate the drug. However, alternative antibiotics are often prescribed without confirming the allergy, largely due to legal concerns regarding re-exposure. Even when a negative challenge test is conducted, non-allergist providers may remain hesitant to reintroduce penicillin. To address the considerable gap between reported and actual penicillin allergies, as well as to ensure the prompt use of penicillins by non-allergists, various management strategies have emerged in recent years. Although several comprehensive reviews have examined these strategies, selecting and applying the most suitable for routine practice is

difficult. This narrative review focuses on the most relevant data regarding the efficiency of key penicillin allergy risk assessment tools, particularly those of clinical significance, and discusses their readiness for implementation in non-allergist settings.

Keywords: penicillin allergy management strategies, efficiency, clinical practice

Penicillin allergy epidemiology

Penicillin-induced anaphylaxis was first reported in 1945, and in 1968, the World Health Organization noted a mortality rate of 0.002% associated with anaphylaxis.¹ To date, there has been no increase in the incidence of allergic reactions to penicillins, and evidence indicates that penicillin sensitization diminishes over time with approximately 50% of penicillin-allergic patients losing their sensitivity within 5 years and about 80% within 10 years.^{2,3} Nevertheless, penicillin allergy is the most commonly reported drug allergy, with prevalence estimates ranging from 6% to 31% across different populations and geographic areas.⁴⁻⁷ Despite this, research indicates that between 77% and 99% of individuals labeled as penicillin-allergic can tolerate penicillins.^{6,8,9}

Penicillin allergy diagnosis typically involves skin tests, blood tests for the identification of specific immunoglobulin E, and drug provocation tests (DPT) which are usually conducted by allergy specialists.^{10,11} However, a global shortage of trained allergists limits access to these evaluations, leading to many individuals being inaccurately classified as penicillin-allergic based on self-reports.¹²

Clinical implications of being labeled as allergic to penicillins

Patients with a documented β -lactam allergy are significantly less likely to receive cefazolin, with a likelihood nine times lower, and are more frequently prescribed non- β -lactam antibiotics perioperatively by non-allergists.¹³ A study from Thailand revealed that allergists are more inclined to confirm penicillin allergies and show less concern about the potential cross-reactivity with third- and fourth-generation cephalosporins compared to non-allergists. The study also found that non-allergists often prescribe alternative antibiotics without confirming penicillin allergy status due to concerns over medicolegal issues related to penicillin re-exposure.¹⁴ Additionally, some practitioners remain hesitant to prescribe penicillins even after a negative DPT to penicillins.¹⁵ While avoiding penicillin is warranted in cases of severe, documented reactions like anaphylaxis, many patients with a self-reported penicillin allergy may not have an

immunological sensitivity at all, and therefore should not avoid penicillins.¹⁶ Mislabeling often stems from the misclassification of mild reactions, leading to unnecessary penicillin avoidance.

Penicillin avoidance is associated with poor clinical outcomes, including prolonged hospitalization,¹⁷ and higher readmission rates.¹⁸ Moreover, subjects labeled as allergic to penicillin are at a higher risk for increased mortality and morbidity¹⁹ due to the use of less effective and broader-spectrum antibiotics, such as vancomycin, fluoroquinolones, clindamycin, and macrolides, which carry higher risks of adverse effects like increased rates of gastrointestinal side effects, and risk of QT prolongation (for the macrolides²⁰), and contribute to antimicrobial resistance.¹⁹ Subjects with methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections labeled as penicillin-allergic are often treated with vancomycin which is associated with inferior survival rates, lower cure rates and higher mortality compared to beta-lactams.²¹ The prevalence of penicillin allergy labels in MSSA bacteremia patients is concerning, with up to 25% reporting an allergy.²² Furthermore, non-beta-lactam alternatives, have shown inferior efficacy in treating Gram-negative bacilli infections, contributing to higher rates of clinical failure.²³ In addition to infection outcomes, inaccurate penicillin allergy labeling contributes to increased rates of *Clostridioides difficile* infections²⁰ and surgical site infections.²⁴

Accurate assessment of penicillin allergy is therefore crucial for optimizing antibiotic use, enhancing patient care, and minimizing the risk of complications. The following sections will discuss the current strategies that focus on clinical history elements which aim to enhance allergy documentation and risk stratification in clinical practice.

Current penicillin allergy management strategies

Based on their role in decision-making, disease management strategies or models can be classified as *assistive* in the sense that they generate probabilities without issuing recommendations or *directive* in the sense that they issue recommendations based on the estimated risks to guide physicians in managing clinical situations.^{25–27} In recent years, various penicillin allergy management strategies have emerged to distinguish between individuals with hypersensitivity reactions to penicillins and those without, and to allow administration of penicillins in non-allergist departments. Several comprehensive reviews^{28–32} have been published that explore these strategies but it is currently difficult to choose the most efficient one. Nonetheless, a number of penicillin allergy management strategies emerge as particularly pertinent for clinical application. These primarily rely on risk classification, which is often based exclusively on the severity of the reported

clinical history. They stem from research conducted in the United States (the Blumenthal strategy³³), Australia (the PEN-FAST strategy/score³⁴), and Europe (the European Network on Drug Allergy (ENDA) strategy,³⁵ the Chiriac strategy/score⁶ with its retrained version – the RChiriac-score³⁶ and the Schrüfer strategy³⁷). This review will also examine the Combined-score,³⁶ a tool developed by Ghiordanescu et al. in a study comparing the efficacy of four established strategies – PEN-FAST, Blumenthal, ENDA, and the Chiriac score. The Combined-score was designed to explore the potential for enhancing the performance of penicillin management strategies, making it interesting for assessing potential improvements in the efficacy of existing approaches.

Description of the selected strategies

The directive strategies

The Romano (ENDA),³⁵ and *Blumenthal*³³ strategies were developed as clinical guidelines for inpatient providers and take into account the clinical characteristics of the index reactions to generate risk classes with different management recommendations. ENDA Class 1 includes high-risk non-immediate reactions (NIRs), Class 2 encompasses high-risk immediate reactions (IRs), and Class 3 consists of low-risk NIRs, IRs, and reactions of unknown nature. The ENDA algorithm³⁵ advises against penicillin exposure across all risk classes but allows exposure to 3rd/4th/5th generation cephalosporins either by graded challenge or full dose procedures in risk classes 2 and 3 respectively. In contrast, Blumenthal Class 1 also includes high-risk NIRs, Class 2, high-risk IRs and unknown reactions with no further details, while Class 3 includes low-risk NIRs, mention of allergy to penicillins in the electronic health records (EHR), and unknown reactions in which the patient denies mucosal involvement, skin desquamation, organ involvement, or need for medical evaluation. The Blumenthal algorithm³³ permits penicillin exposure by test-dose procedure solely for Class 3 subjects. Additionally, it allows exposure to 3rd/4th/5th generation Cephalosporins by full-dose procedure in risk Class 2, and to 1st/2nd generation Cephalosporins by full-dose procedure in risk Class 3. The main difference between the two strategies lies in how they classify the "unknown reactions". In the Blumenthal strategy, these are considered high or low risk based on specific anamnestic details, while in the ENDA strategy, they are classified as low risk.

The third directive strategy was originally developed by *Reichel et al.*³⁸ and subsequently refined by *Schrüfer et al.*³⁷ This model, designed by allergists for the use of non-allergists, utilizes five

binary questions to evaluate the characteristics of the hypersensitivity reaction such as its semiology, chronology, and the age at which the initial reaction occurred. Additionally, it incorporates laboratory tests such as liver and kidney biomarkers and the presence of cytopenia. Based on the answers provided, recommendations are made for either delabeling or considering alternative antibiotics. A negative response to a question prompts the inquiry of the next question. A negative answer to all questions (1-5) leads to a recommendation for delabeling. A positive response to any of the first three questions, which address non-specific symptoms (question 1), skin symptoms limited to childhood or adolescence (question 2), and urticaria/angioedema during treatment with recurrence after discontinuing penicillins (question 3) leads to a recommendation for delabeling. Conversely, affirmative answers to questions four and five, which pertain to maculopapular exanthema (MPE) occurring during or within a week after stopping penicillin exposure (question 4) and reactions such as urticaria and anaphylaxis occurring within 30 minutes of exposure, along with clinical or laboratory indicators of a severe non-immediate reaction or reactions during systemic anaesthesia (question 5) result in a recommendation to avoid penicillins and consider alternative antibiotics. This approach significantly contrasts with the ENDA³⁵ and Blumenthal³³ strategies in two key aspects. First, in subjects with angioedema that occurs during treatment but also after its cessation, it recommends delabeling whereas the other directive strategies label angioedema occurring during exposure as high-risk without considering additional clinical information and recommend avoidance of penicillins. Second, the Schrüfer strategy³⁷ recommends penicillin avoidance in patients with a history of MPE occurring during or within one week after stopping treatment with penicillins, an approach employed by the other two strategies in high-risk patients.^{33,35} Nevertheless, the other two strategies deem MPE as low-risk.^{33,35} Table 1 summarizes the key similarities, differences, and recommendations of the directive strategies.

The assistive strategies aim to support clinicians in making data-driven risk predictions while not offering any patient management instructions.

*The PEN-FAST score*³⁴ assigns a score between 0 and 5 to patients based on three clinical criteria: the semiology of reaction (anaphylaxis, angioedema, or SCAR receive 2 points), the time elapsed since the reaction (less than five years receives 2 points), and information about any pharmacological treatment (1 point if treatment was given). PEN-FAST scores of 4-5 indicate a high risk of a positive penicillin test at 50%. A score of less than 3 is indicated for delabeling.

The *Chiriac-score*⁶ incorporates several clinical history variables, including the presence of anaphylaxis as the index reaction, the age at which the reaction occurred, the number of prior events in the clinical history, the chronology of the reaction, the time interval since the drug hypersensitivity reaction, and the culprit beta-lactam. This score was originally developed for patients experiencing reactions to both penicillins and cephalosporins. Subjects with severe cutaneous adverse reactions (SCAR) were excluded from the training cohort.⁶ Ghiordanescu et al. subsequently retrained the model on a different cohort which included SCAR patients to specifically predict penicillin allergy, resulting in a new score referred to as the *RChiriac-score*.³⁶ The *Combined-score*³⁶ was developed on a retrospective cohort by pooling all variables from the ENDA,³⁵ Blumenthal,³³ PEN-FAST³⁴ and Chiriac strategies.⁶ The authors then conducted a variable selection process to establish a final model which included the semiology and chronology of the DHR, 5-year time since the DHR indicator, age at the time of the reaction, and treatment indicator. A comparative analysis of the ENDA,³⁵ Blumenthal,³³ Schrüfer,³⁷ and PEN-FAST³⁴ strategies is illustrated in **Figure 1**.

Table 1. ENDA, Blumenthal and Schrüfer strategies, classification by risk class and corresponding recommendations.

	Risk class	Clinical presentation	Recommendations
ENDA	<u>Class 1</u> High-risk NIR	SCARs, generalised bullous FDE, severe MPE, linear IgA bullous dermatosis, systemic vasculitides, organ involvement/cytopenia, penicillin-induced autoimmune disease	avoid using Penicillins/Cephalosporins OR use non-BL antibiotics by microbial coverage OR use, upon graded challenge, Aztreonam, Carbapenems, 3rd/4th/5th generation Cephalosporins
	<u>Class 2</u> High-risk IR	anaphylaxis, hypotension, laryngeal oedema, bronchospasm, urticaria or angioedema, generalised angioedema	avoid using Penicillins/Cephalosporins OR use non-BL antibiotics by microbial coverage OR use, upon graded challenge, Aztreonam, Carbapenems, 3rd/4th/5th generation Cephalosporins
	<u>Class 3</u> Low-risk IR, NIR, and unknown reactions	NIR: contact dermatitis, systemic contact dermatitis, local reaction (i.m. administration), exfoliative palmar dermatitis, FDE, delayed urticaria, mild or moderate MPE, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) OR IR: isolated generalised pruritus which did not require treatment, isolated digestive symptoms, localised urticaria OR unknown reactions	avoid using Penicillins/Cephalosporins OR use full-dose Aztreonam, Carbapenems, 3rd/4th/5th generation Cephalosporins OR use non-beta-lactam (BL) antibiotics by microbial coverage
Blu	<u>Class 1</u> High-risk NIR	Stevens-Johnsons syndrome, Toxic Epidermal Necrolysis, Acute interstitial Nephritis, Drug Rash Eosinophilia with Systemic Symptoms (DRESS), haemolytic anaemia	avoid using Penicillins/Cephalosporins, and Carbapenems AND use alternative agents by microbial coverage;

BL – beta-lactam, EHR – electronic health records, FDE – fixed drug eruption, MPE – maculopapular exanthema, SCAR – severe cutaneous adverse drug reaction, IR- immediate reactions, NIR – non-immediate reactions. Adapted after Ghiordanescu et al. Comparative Performance of 4 Penicillin-Allergy Prediction Strategies in a Large Cohort. The Journal of Allergy and Clinical Immunology: In Practice. Published online July 2024:S2213219824007438. doi:10.1016/j.jaip.2024.07.012

	Class 2 High-risk IR and unknown reactions	anaphylaxis, angioedema, wheezing, laryngeal oedema, hypotension, hives/urticaria OR unknown reactions with no further details available from patient/proxy	avoid using the penicillin subclass OR use 3rd/4th/5th generation Cephalosporins by test dose procedure OR use alternative agent by microbial coverage OR use Aztreonam or Carbapenems
	Class 3 Low-risk NIR, EHR and unknown reactions without severity elements	MPE, or minor rash (not hives), EHR mention but patient denies, unknown reaction, but patient denies mucosal involvement, skin desquamation, organ involvement, or need for medical evaluation	use full dose Cephalosporins OR use Penicillin by test dose procedure OR use Carbapenems
Schrüfer	Question 5 High-risk IR and NIR and reaction during general anaesthesia	chronology of up to 30 minutes from exposure to reaction and a semiology of urticaria or anaphylaxis. signs and symptoms of anaphylaxis occurrence during general anaesthesia mucous membrane erosions/skin bullae hepatic or renal involvement or cytopenia	If answer is Yes/Uncertain – USE ALTERNATIVE ANTIBIOTIC
	Question 4 MPE	measles-like rash or MPE occurring during or within one week of penicillin exposure?	If answer is Yes – USE ALTERNATIVE ANTIBIOTIC (as for high-risk subjects)
	Question 3 Recurrent acute urticaria	acute urticaria with or without angioedema during penicillin exposure which reoccurs for several days after treatment is stopped?	If answer is Yes – DELABEL
	Question 2 Skin involvement during childhood/adolescence	skin symptoms such as urticaria and MPE only developed during or immediately after stopping penicillin exposure occurring during childhood or adolescence (less than 16 years)?	If answer is Yes – DELABEL
	Question 1 Complaints and timing not compatible with hypersensitivity	symptoms reported are not compatible with a hypersensitivity reaction – gastrointestinal symptoms, cephalaea, palpitation? chronology between exposure and symptom onset not suggestive of hypersensitivity – urticaria >2 days after the last dose; MPE >7 days after the last dose?	If answer is Yes – DELABEL

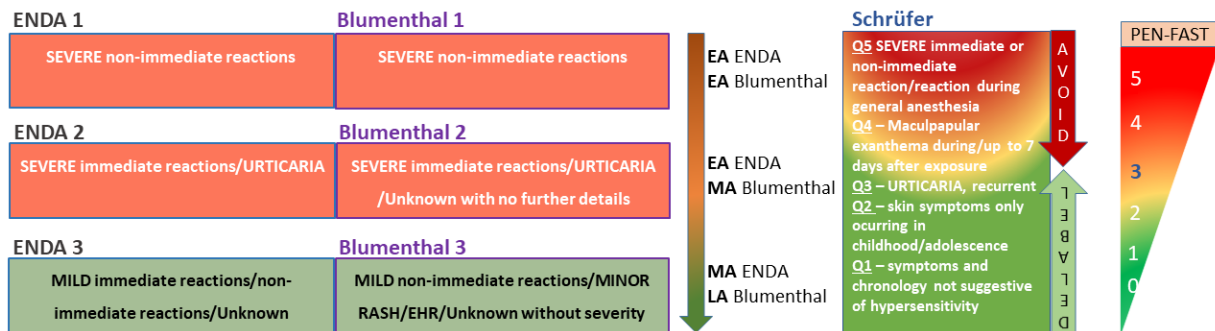


Figure 1. Red colour indicates high-risk, yellow represents medium-risk, and green signifies low-risk. The Schrüfer strategy does not specifically define risk classes but recommends delabeling in subjects with affirmative answer to questions 1-3 (graphically associated with green colour) while it recommends avoidance in subjects with affirmative answers to question 5 (graphically associated with red colour). Question 4 appears highlighted in yellow in the original publication. The PEN-FAST scores 4-5 are high-risk (50%), 3 is moderate-risk (20%), 1-2 are low-risk (5%), 0 is very-low-risk of positive penicillin test (<1%). The suggested cut-off for delabeling is 3.

Abbreviations - EA = Extensive avoidance, EHR = electronic health records, MA = Moderate avoidance, LA = Limited (Selective) avoidance.

Adapted after Ghiordanescu et al. Comparative Performance of 4 Penicillin-Allergy Prediction Strategies in a Large Cohort. The Journal of Allergy and Clinical Immunology: In Practice. Published online July 2024:S2213219824007438. doi:10.1016/j.jaip.2024.07.012

The efficiency of the selected strategies

When selecting an appropriate clinical model, it is important to carefully consider critical parameters such as the classification of low-risk patients, sensitivity, specificity, and rates of misclassification. By calculating local prevalence, clinicians can determine positive and negative predictive values (PPVs and NPVs), which decisively inform their assessment of acceptable risk levels — a threshold that varies significantly across specialties and available medical resources. Lower true allergy prevalence can undermine the reliability of high NPVs while the positive PPVs decline alongside reduced penicillin allergy prevalence. Therefore, diagnostic tools must be evaluated on a sufficiently large cohort of confirmed allergic patients to ensure accurate NPVs results.

The *ENDA*³⁵ and *Blumenthal*³³ strategies underwent external validation within a retrospective cohort comprising 1884 subjects with a history of hypersensitivity reactions to penicillins presenting at the Allergy Unit of the University Hospital of Montpellier, where the prevalence of positive allergy tests (skin tests or drug provocation tests) was recorded at 20.3%.³⁶ This prevalence aligns with previous findings from the same research group,⁶ yet it is notably higher than results reported in studies conducted in the United States³ and Australia.^{34,39} In this study, both strategies showed considerable overlap in their classification of low-risk subjects, with 44.5% of cases falling into ENDA class 3 and 38.0% into Blumenthal class 3. The sensitivity rates were also similar, recorded at 76.0% for ENDA and 77.0% for Blumenthal, although their specificities were significantly lower, with ENDA at 50.0% and Blumenthal at 42.0%. The NPVs for the ENDA and Blumenthal methods were found to be 89.0% and 88.0%, respectively, while the PPVs were 28.0% for ENDA and 25.0% for Blumenthal. By design, these strategies were safe, as none of the subjects with positive outcomes and a history of anaphylaxis, severe cutaneous adverse reactions (SCAR), or other severe non-immediate reactions (such MPE with fever alone, severe/generalised MPE with extensive desquamation, mucosal lesions alone, vasculitis, serum sickness-like disease, purpura, isolated cytopenia, isolated hepatic involvement) were misclassified. Nevertheless, the ENDA strategy has resulted in unnecessary avoidance for 79.7% of subjects. Conversely, the Blumenthal strategy leads to unnecessary avoidance in 46.4% of the cases. The authors comment that, although the ENDA and Blumenthal strategies may not classify as many patients as low-risk, their high sensitivity renders them safe for clinical application by non-allergists. However, by increased unnecessary avoidance they can compromise individual and public health outcomes.³⁶

The *directive strategy* developed by *Reichel et al.* was applied to a cohort of 200 patients presenting at the Allergy Department of the University Hospital Würzburg with previous reactions to various antibiotics, including beta-lactam antibiotics. However, the study design raises several questions regarding its methodological approach. Notably, not all patients were investigated for their hypersensitivity status, and in cases where investigations were conducted, some patients were re-exposed to chemically related antibiotics rather than the actual culprit drug, which questions the clinical relevance of the outcome and external validity of these findings. The strategy was later refined by *Schrüfer et al.*³⁷ and applied to a cohort of 800 subjects from Germany with suspected hypersensitivity to beta-lactam antibiotics in which the positive outcome prevalence (positive skin tests, specific IgEs or DPT) was 25.6% which is similar to that of the Montpellier cohort.³⁶ The refined strategy recommended delabeling in 41.0% of the cases and exhibited a sensitivity of 90.0%, and a specificity of 56.0% which were comparable with the other two directive strategies. Of the subjects with positive outcome, 10.0% (n=21) have been misclassified. Of these 8 (representing 2.6% of the total subjects receiving a recommendation for delabeling) had a clinical history of anaphylaxis. This raises concerns about the sensitivity of question 5 in accurately identifying anaphylaxis within the clinical history. The NPV and PPV were 94.0% and 41.0%, respectively. Unnecessary avoidance occurred in 44.5% of cases. Schrüfer's research found that among the 195 patients who answered affirmatively to question 4, 106 (54.3%) had a positive allergy outcome. However, the authors relied on allergy test results as a proxy for actual allergy status, which may have led to an overestimation of clinically relevant sensitization in some low-risk patients with MPE who only underwent skin testing. This issue was similarly noted as a limitation in the study by Ghiordanescu et al.³⁶ Given that MPE is a mild, manageable reaction, it is questionable whether the Schrüfer strategy advising penicillin avoidance and referral for additional allergy testing is appropriate, particularly considering the strain it places on an already overwhelmed specialty for a condition that is generally manageable.

The *PEN-FAST assistive strategy* (score) was derived using a prospective cohort from Melbourne of 622 patients with reported allergy to penicillins, where the outcome prevalence (positive skin tests or DPT) was 9.3%.³⁴ The original strategy, which uses a threshold of less than 3, demonstrated a sensitivity of 70.7% and a specificity of 78.5%, along with a NPV of 96.3% and a PPV of 25.3%. At this threshold, 17 out of 460 low-risk patients (3.7%) have been misclassified. The derived cohort in Melbourne was validated on three cohorts from Nashville, Sydney, and Perth³⁴ which had

outcome prevalences of 19.0%, 27.0%, and 48.0%, respectively. The sensitivity and specificity for these cohorts were 73.7% for Nashville, 70.4% for Sydney, and 87.5% for Perth. The NPVs varied across these cohorts, ranging from 84.9% to 98.4%. Except for the PALACE study,⁴⁰ which is a randomized controlled trial, the validation of the PEN-FAST algorithm was performed in retrospective cohorts.^{41–45} In the cohorts from Su et al.,⁴² Piotin et al.,⁴¹ Castagna et al.,⁴⁴ and Gonzalez-Estrada et al.,⁴³ outcome prevalences ranged from 2.0% (Gonzalez-Estrada's Mayo non-enriched test) to 66.2% (Piotin). Sensitivity varied across these cohorts, from 23.3% (Gonzalez-Estrada's Mayo enriched test) to 100% (Su et al.), while specificities ranged from 56.0% (Piotin) to 81.6% (Gonzalez-Estrada's Mayo enriched training). The NPVs for these studies varied between 75.4% (Gonzalez Estrada's Mayo enriched test) and 100% (Su et al.). PEN-FAST was found to be unreliable in pediatric populations under 12 years of age, showing a sensitivity of 57.0%, a specificity of 45.7%, and an NPV of 95.0%. This conclusion was drawn from a study involving 2031 allergy labels, which had an outcome prevalence of 5.3%.⁴⁵ In the study by Ghiordanescu et al.,³⁶ PEN-FAST strategy demonstrated sensitivity and specificity rates of 66.0% and 73.0%, respectively, which are consistent with the original publication's findings.³⁴ In this particular study, PEN-FAST identified 65.0% of the subjects as low-risk for allergies. However, 33 patients with a severe index reaction (anaphylaxis, other severe non-immediate reactions) were incorrectly classified as low-risk, representing 3.0% of all low-risk patients. The NPV for a PEN-FAST score of less than 3 was 90.0%, suggesting its usefulness as a rule-out test, though this was slightly lower than reported in previous studies.^{40–43} This discrepancy may be due to the higher prevalence of positive outcomes (20.3%) in Ghiordanescu et al.'s cohort,³⁶ compared to the 9.3% in the original study.³⁴ Additionally, differences in participant characteristics could have influenced the algorithm's performance. While the original study excluded cases categorized by Ghiordanescu's study as Other severe non-immediate reactions, excluding these cases from the analysis, did not notably affect the NPV, which remained at 90.0%. For comparison, the retrospective cohorts from Piotin et al.⁴¹ and Su et al.⁴² focused only on subjects with immediate reactions, while the PALACE study⁴⁰ excluded participants with anaphylaxis and severe non-immediate reactions.

The *original Chiriatic* score⁶ was derived using a retrospective cohort of 1991 subjects and externally validated on a prospective cohort of 200 subjects from Southern France, undergoing investigations for hypersensitivity to beta-lactams (penicillins and cephalosporins). Subjects with SCAR were excluded from the cohort used to develop the model. The prevalence of outcomes

(positive skin tests or DPT) differed between the retrospective and prospective cohorts, at 23.6% and 31.0%, respectively. The PPVs were 40.0% in the retrospective cohort versus 57.0% in the prospective cohort, while the NPVs were 83.0% and 82.0%, respectively. The misclassification rates were similar between the two cohorts, at 19.4% for the retrospective cohort and 21.0% for the prospective cohort. Among the misclassified patients, 13 (3.1%) experienced anaphylaxis during allergy testing. The *RChiriatic score*³⁶ demonstrated an AUC of 0.77 with a sensitivity of 55.0% and a specificity of 85.0% at Youden's index. The NPV and PPV for these coordinates were 88.0% and 49.0% respectively. The authors assessed various thresholds for predicted probabilities to classify patients as low risk, resulting in 46.0% to 77.0% being categorized in this way, with sensitivity ranging from 55.0% to 80.0% and specificity from 53.0% to 85.0%. The model misclassified between 14 and 53 patients who experienced severe reactions, representing 2.0% to 4.0% of those identified as low risk.

The *Combined-score* had an AUC of 0.80 with a sensitivity of 57.0% and a specificity of 91.0% at Youden's index.³⁶ The NPV and PPV for these coordinates were 89.0% and 62.0% respectively. As for the *RChiriatic-score*,³⁶ the authors assessed various thresholds for predicted probabilities to classify patients as low risk, resulting in 50.0% to 82.0% being categorized in this way, with sensitivity ranging from 57.0% to 80.0% and specificity from 58.0% to 91.0%. Five to 28 patients with severe index reactions were misclassified by the model, which represents less than 1.0% to 2.0% of the low-risk cohort. In the comparison conducted by Ghiordanescu et al,³⁶ the performance of the *Combined-score* was largely comparable to that of the *PEN-FAST* and *RChiriatic* scores. This indicates that enhancements to penicillin allergy risk stratification tools, even when customized for particular populations or local penicillin allergy incidences are probably not feasible. Overall, the scoring strategies demonstrate effective delabeling capabilities; however, this comes at the cost of an increased number of misclassified positive subjects exhibiting high-risk index reactions.³⁶ A detailed comparative analysis of the *PEN-FAST* and *Chiriatic* score derivation and validation cohorts is available in the supplementary materials of the publication by Ghiordanescu et al.³⁶

Challenges in managing Penicillin Allergy

Delabeling of penicillin allergy is influenced by the patient's risk profile.^{30,46} In high-risk subjects, a comprehensive approach combining clinical history, laboratory tests, and drug provocation challenges is essential for an accurate diagnosis of penicillin allergy.⁴⁶ While testing for penicillin-specific IgE antibodies can assist in diagnosing penicillin hypersensitivity, the method has limited

sensitivity and specificity.⁴⁷ In vitro and in vivo (skin tests) to penicillins are usually performed by allergy specialists.⁴⁶ In contrast, in low-risk populations, graded oral or intravenous drug challenges are considered the diagnostic gold standard.⁴⁸ These are currently mainly performed in inpatient settings which have the best evidence for optimizing antibiotic use.⁴⁹ Nevertheless, their safety of use in outpatient settings has also been recently demonstrated.^{32,46} Research shows that 96% of low-risk patients can be effectively delabeled through graded challenges,⁵⁰ whereas skin testing achieves a success rate of only 88%, particularly in low-risk groups with non-immediate reactions where the predictive value is decreased.⁵¹ Additionally, detectable serum IgE levels against penicillins may be found in subjects whose clinical histories do not indicate an IgE-mediated allergic response, therefore their use in a population low-pretest probability is questionable.⁴⁹ However, in clinical practice, low-risk non-immediate reactions often present challenges in classification across different strategies, as well as in recommendations for exposure avoidance. For example, the authors of the Schrüfer strategy comment that although MPE is generally regarded as low-risk for certain phenotypes there is a considerable chance for a positive challenge. Conversely, the ENDA and Blumenthal strategies classify MPE as low-risk with recommendations for moderate or limited avoidance, respectively. It is nevertheless important to note that the ENDA strategy considers a particular phenotype of MPE - the severe MPE as high-risk. Still, the literature lacks clear stratification of severity for MPE, aside from references to body surface coverage greater than 50%, which is associated with MPE in DRESS syndrome, or the presence of bullae.⁵² Furthermore, patients may struggle to accurately describe papular eruptions, leading to potential diagnostic difficulties. In addition, clinical recognition of these reactions can be challenging, and healthcare providers themselves might require proper training.

Discussions

Implementing penicillin allergy delabeling strategies, which use clinical predictors to stratify risk, is an important step toward optimizing both individual patient care and public health outcomes. Clinical history predictors play a crucial role in structuring the allergy assessment and ensuring that best practices are followed throughout the testing process. However, despite advancements over the past decade, none of the chosen strategies that are particularly significant for clinical practice appear to achieve an ideal equilibrium between safety and unnecessary avoidance. Moreover, significant improvements in the accuracy of these tools based solely on clinical history are unlikely as shown by the Combined-score performance.³⁶ Therefore, when choosing a tool for

a specific clinical setting, it's essential to consider factors like the type of clinic, which influences the prevalence of penicillin allergies and symptom distribution.

Since none of the strategies has proven perfectly balanced, the following pathway involving two filters can be followed by non-allergists in cases where emergency treatment with beta-lactam antibiotics is necessary. The directive strategies can be applied as a first step to assess the risk class to which a patient belongs. The ENDA and Blumenthal strategies, unlike the Schrüfer strategy, which recommends alternative antibiotics without providing details on the potential use of cephalosporins, carbapenems/aztreonam, or even penicillins with different side chains, have the advantage of offering embedded guidance based on the risk class with available antibiotic replacements. High-risk patients with medium or extensive avoidance recommendations can later be referred for allergy testing. Nevertheless, in emergencies involving high-risk patients where cross-reactive antibiotics may be required, it is advisable to seek telephone guidance or direct consultation from an allergist, and possibly conduct urgent skin testing before administering antibiotics. For low-risk patients, any of the scoring strategies (PEN-FAST, Chiriatic/RChiriatic score, or the Combined score), which are highly efficient for delabeling, can be employed to verify if the patient is indeed low-risk also according to these strategies. If this is the case, the patient can be safely delabeled and administered the antibiotic according to their needs, under surveillance. A potential pathway to follow by non-allergists is depicted in **Figure 2**. Evidence is accumulating that, regardless of the tool or definition of low-risk, direct challenges to confirm penicillin allergy are increasingly safe and accessible.⁵³ However, it should be noted that the existing tools are not flawless, and there is no absolute guarantee that patients will not react upon re-exposure to penicillins. Non-allergist practitioners must therefore remain aware of the potential risks and be prepared to manage both severe and non-severe hypersensitivity reactions in collaboration with their teams.

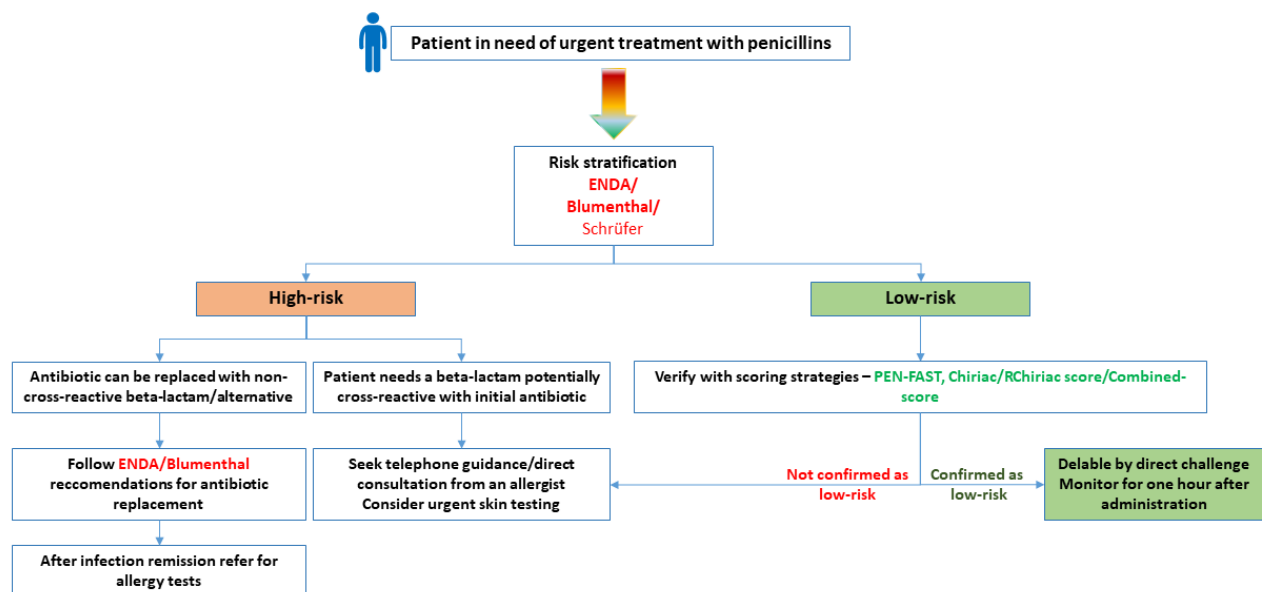


Figure 2. Suggested pathway for the management of patients labeled as allergic to penicillins in non-allergist settings

Conclusions

Penicillin allergy management strategies can increase the use of penicillin antibiotics in patients with a history of reactions to penicillins. However, there is still uncertainty about whether these strategies can effectively reverse the negative outcomes associated with penicillin allergy labels.

Critical questions persist about the optimal strategies for specific clinical contexts, as well as the logistical considerations necessary for their successful implementation in clinical practice. Currently, the strategies analyzed in this review do not appear to be ready for widespread application on their own, and further advancements relying solely on clinical history are unlikely to yield substantial improvements. Despite ongoing systematic reviews evaluating their efficiency, a shift in research focus may be necessary, emphasizing the identification of novel biomarkers. Therefore, it is crucial to pursue a thorough investigation of in vitro and ex vivo methods aimed at discovering new allergy biomarkers, particularly those related to beta-lactam antigenic determinants.

Alergia la penicilină este cea mai frecvent raportată alergie la medicamente, cu rate de prevalență variind de la 6% la 31% în diferite populații și zone geografice. Alergiei la penicilină este legată de rate mai mari de mortalitate și morbiditate, internări prelungite în spital, rate crescute de reinternare și o dependență mai mare de antibiotice. Cercetările indică faptul că aproape 99% dintre cei alergici la penicilină pot tolera medicamentul. Cu toate acestea, antibioticele alternative

sunt adesea prescrise fără a confirma alergia, în mare parte din cauza preocupărilor legale cu privire la reexpunere. Chiar și atunci când se efectuează un test de provocare negativ se ezită să reintroducă penicilina. Pentru a aborda decalajul considerabil dintre alergiile raportate și cele reale la penicilină, precum și pentru a asigura utilizarea promptă a penicilinelor, în ultimii ani au apărut diverse strategii de management. Deși mai multe analize cuprinzătoare au examinat aceste strategii, selectarea și aplicarea celor mai potrivite pentru practica de rutină este dificilă. Această review se concentrează pe cele mai relevante date cu privire la eficiența instrumentelor cheie de evaluare a riscului de alergie la penicilină, în special pe cele cu semnificație clinică, și discută gradul de pregătire a acestora pentru implementare.

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