

A Retrospective Critical Analysis and Risk Stratification of Penicillin Allergy Delabeling in a UK Specialist Regional Allergy Service



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What is already known about this topic? A spurious label of penicillin allergy (Pen-A) is a major public health problem and increases health care costs.

What does the article add to our knowledge? This is the first British study to critically characterize and risk stratify patients with a label of Pen-A and highlights the potential role for a direct supervised penicillin challenge in patients least likely to have Pen-A.

How does this study impact current management guidelines? This study provides proof-of-concept data regarding the potential role for a computerized decision support system in identifying “low risk” patients carrying a Pen-A label who would be suitable for a direct supervised penicillin challenge.

BACKGROUND: A spurious label of penicillin allergy (Pen-A) negatively impacts on antibiotic stewardship and health care costs. Recent studies have proposed a guideline-steered direct penicillin challenge without undertaking allergy tests when “true allergy” is unlikely.

OBJECTIVE: To critically analyze Pen-A clinical presentation, perform risk stratification, and determine clinical predictors for “true allergy.”

METHOD: Data were extracted retrospectively from clinical and electronic patient records.

RESULTS: A total of 231 patients (M = 82; F = 149; mean age 51.22 [standard deviation $\pm$ 18.07] years) were analyzed. Based on clinical history, patients were categorized as likely type I hypersensitivity reaction (HSR) (n = 27), likely type IV HSR (n = 65), indeterminate (n = 111), and HSR unlikely (n = 28). Based on an index reaction and comorbidities, patients were classified into “low risk” (n = 143) and “high risk” (n = 78).

Pen-A was excluded in 74% of patients assessed having likely type I HSR, 91% with likely type IV HSR, 93% of indeterminate, and 100% of HSR unlikely patients. The negative predictive value for successful delabeling in the “low risk” group was 94% (odds ratio [OR] = 2.9; P = .02). Predictors for “true Pen-A” were history of anaphylaxis (OR = 30.6; P < .001), hospitalization (OR = 7; P < .001), $\leq$ 5 years since the index reaction (OR = 3; P = .04).

CONCLUSIONS: Systematic clinical characterization and risk stratification has an important role in Pen-A delabeling. These data provide proof of concept for a guideline-based selection of patients labeled with Pen-A for a direct penicillin challenge. Patients in the “low risk” group seem suitable for this intervention, although a rigorous prospective evaluation is needed in a multicenter study. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:251-8)

Key words: Penicillin allergy; Antibiotic stewardship; Delabeling; Anaphylaxis; Hypersensitivity

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Up to 10% of the population carry a label of penicillin allergy (Pen-A).^{1,2} However, 90% to 99% of patients are deemed not to be allergic after comprehensive allergy tests.³⁻⁶ Currently used British Society for Allergy and Clinical Immunology (BSACI) Pen-A diagnostic workup is labor intensive, time consuming, resource dependent and requires allergy specialist input.⁷ Given the demand for allergy services in the United Kingdom⁸ and other countries,⁹ and the huge burden of the problem, a significant majority of patients receive second-line antibiotics for the treatment of infections, thus having an adverse impact on antibiotic stewardship.^{10,11}

Recent studies have shown that a Pen-A label is associated with higher health care costs, higher rates of surgical site infections,

Abbreviations used

BSACI- British Society for Allergy and Clinical Immunology
 CDSS- Clinical decision support system
 CSUA- Chronic spontaneous urticaria and angioedema
 EAACI- European Academy of Allergy and Clinical Immunology
 HEFT- Heart of England NHS Foundation Trust
 HSR- Hypersensitivity reaction
 IDT- Intradermal test
 MDM- Minor determinant mix
 NHS- National Health Service
 NPV- Negative predictive value
 OR- Odds ratio
 Pen-A- Penicillin allergy
 SSiGE- Serum specific IgE

longer hospital stay, and higher readmission rates.^{1,10-12} Furthermore, a label of Pen-A increases the risk of antibiotic resistance and is associated with higher rates of hospital-acquired infections including methicillin-resistant *Staphylococcus Aureus*, *Clostridioides difficile*, and vancomycin-resistant enterococci.¹⁰ Hence, there is a real need for a safe and rapid mechanism to administer penicillin/s to those who are least likely to be allergic.

The reference standard to confirm penicillin tolerance is an oral challenge with a therapeutic dose. Direct oral challenges in “low risk” individuals are being more widely used around the world.¹³⁻¹⁵ There has been a drive towards a guideline-based direct administration of penicillin/s (without undertaking allergy tests) to those who are least likely to be allergic.¹⁶⁻¹⁸ This has been recommended as a concerted multidisciplinary team approach comprising allergy specialists, microbiologists, infectious diseases specialists, nurses, internists, and pharmacists.^{11,19} This involves obtaining a standardized drug allergy history linked to a clinical algorithm with the aim of identifying those who are most unlikely to be truly allergic. Implementation of such an approach by the Harvard group of hospitals alone has estimated to produce cost savings of \$8.9 to \$13.7 million USD in the first year.¹¹

Clinical characterization and risk stratification of patients is key to the success of this approach but potential barriers are availability of reliable historical information from clinical records and the patient’s recall of the “index episode.” Data regarding clinical characterization, risk stratification, and outcomes of Pen-A tests are key to designing safe clinical systems involving “direct” Pen-A delabeling (ie, without undertaking allergy tests in patients least likely to be allergic) and robust antibiotic stewardship protocols. This may differ between countries due to potential variations in patient demographics, health service framework, referral patterns, and local antibiotic stewardship policy, and there is paucity of such a dataset in the UK National Health Service (NHS).

The main objective of this study was to perform a retrospective critical analysis of index reactions to penicillin/s in patients carrying a Pen-A label and correlate these to the outcomes of a systematic and standardized allergy workup in a regional UK NHS specialist allergy service.

METHODS**Patient selection**

Patients were identified from the department database. The cohort included 231 consecutive adult patients with suspected

Pen-A, evaluated in our specialist regional allergy center at Heart of England NHS Foundation Trust (HEFT), Birmingham, United Kingdom between 2008 and 2018 (Figure 1).

Allergy tests

All patients were formally assessed by an allergy specialist and underwent detailed evaluation of clinical history, scrutiny of previous prescription record when needed, skin prick tests, intradermal tests (IDT), and serum specific IgE (SSiGE) measurement. Our standard skin test panel comprises benzylpenicilloyl-poly-L-lysine (major determinant) and minor determinant mix (MDM) (DAP kit; Diater, Madrid, Spain), benzylpenicillin, amoxicillin, and any other penicillin that was implicated in the index reaction. Where there was no evidence of sensitization, a supervised graded penicillin challenge procedure was carried out. Our protocols for skin tests and challenge procedure are in accordance with the BSACI and European Academy of Allergy and Clinical Immunology (EAACI) guidelines for investigations and management of immediate (type I) and non-immediate (type IV) hypersensitivity reactions (HSRs) to penicillin.^{7,20,21}

Drug challenge tests

These were carried out to exclude type I HSR in all patients with no demonstrable sensitization. The penicillin implicated in the index reaction was employed for the challenge procedure (eg, cumulative dose of 505 mg of phenoxymethylpenicillin or 505 mg of amoxicillin or flucloxacillin) when this information was available. In all other cases, where the nature of penicillin implicated in the index reaction was not available, the challenge procedure was carried out either with amoxicillin or co-amoxiclav (cumulative amoxicillin dose of 505 mg). Patients were advised to continue with the medication for 2 days (equivalent to 250 mg twice daily of amoxicillin) when there was a history suggestive of a nonimmediate (type IV) HSR or in cases where the clinical history was classified as “indeterminate.” Patients were followed up to enquire regarding occurrence of a nonimmediate HSR.

Patient selection criteria for Pen-A testing

Our criteria for Pen-A testing are in accordance with BSACI guidelines⁷ with occasional exceptions—offered to those with a label of “multiple antibiotic allergy” (including a label of Pen-A), those with a label of Pen-A with frequent or recurrent infections and/or high risk for infections such as bronchiectasis, immunodeficiency, cystic fibrosis, diabetes mellitus, and hyposplenism, in those with a label of Pen-A requiring a specific beta-lactam [eg, endocarditis, syphilis, etc], and in the context of anaphylaxis during general anesthesia when penicillin/s are implicated alongside other drugs/agents. A risk-benefit analysis is undertaken for each case, and patient preference/circumstances are factored into the decision-making process for those being considered for Pen-A tests. Patients with a clear recent history of penicillin(s)-induced anaphylaxis and those with a clear history of recurrent penicillin(s)-induced anaphylaxis are usually given a clinical diagnosis (Pen-A tests are not offered) as per our local protocol and advised regarding appropriate avoidance measures.

Data collection

Data were extracted retrospectively from clinical and laboratory records and entered in a spreadsheet (Microsoft Excel 2016). To ensure consistency and quality assurance, data extraction was carried out by a single operator (OEM). Demographic data (age and gender) and the following clinical variables were systematically extracted

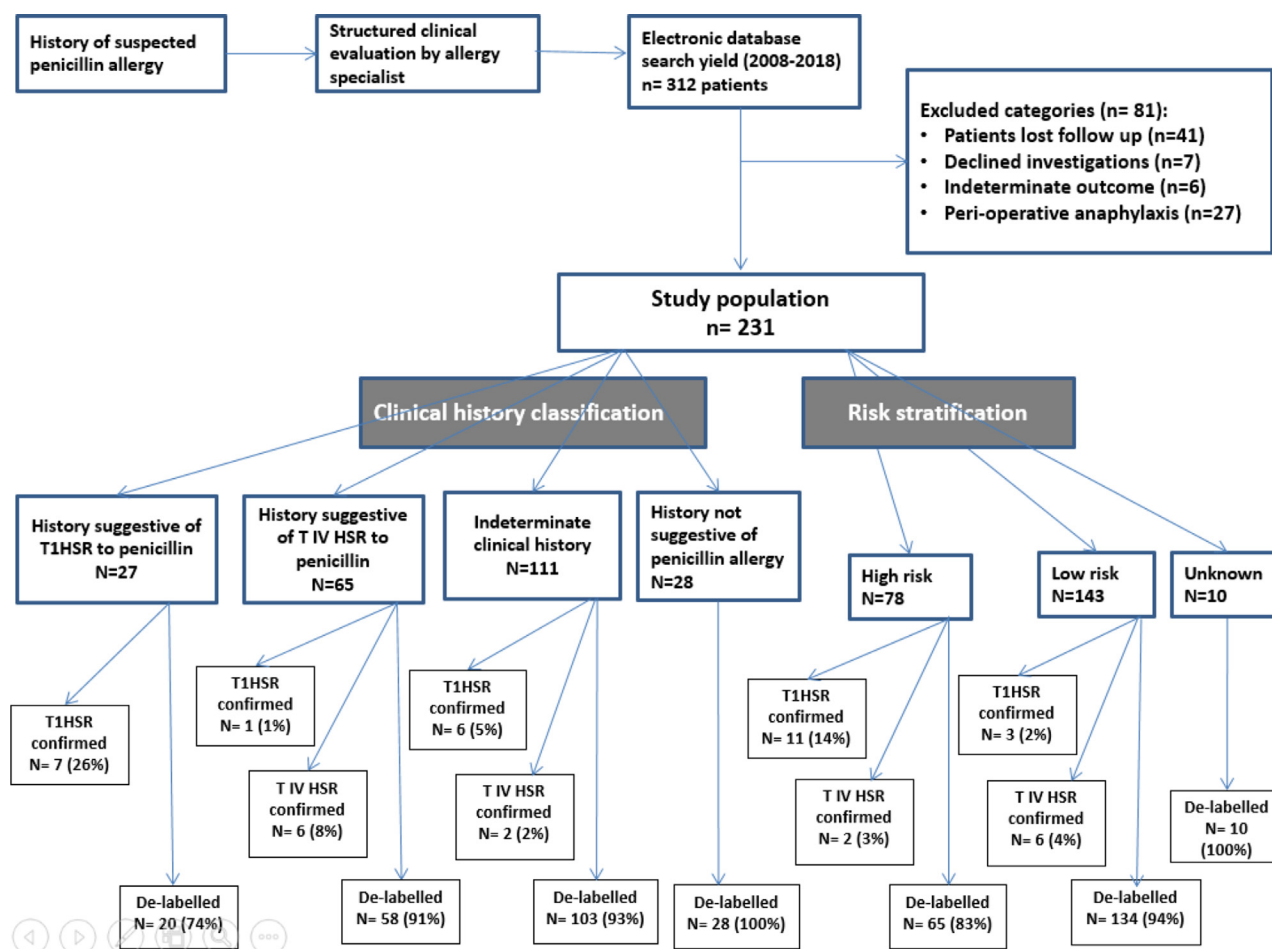


FIGURE 1. Study flow diagram. In patients with confirmed type I hypersensitivity reaction (T1HSR) to penicillin ($n = 14$), 6 were diagnosed with a positive intradermal test, 3 had a positive serum specific IgE, and 5 patients had a positive supervised challenge. Half of all confirmed T1HSRs (7/14) did not have a presenting history suggestive of T1HSR; the remaining 7 patients presented with an “indeterminate history” ($n = 6$) and history of “likely type IV HSR” ($n = 1$). Application of the risk stratification module (Table II) in these 14 cases; the majority (79% [$n = 11$]) were categorized as “high risk.”

from clinical and laboratory records: suspected culprit penicillin, details of the allergic reaction including temporal association, characterization of symptoms and severity, time elapsed since the index event, outcome of Pen-A tests (skin tests, SSiGE, and challenge tests), cardiorespiratory comorbidities, and history of concomitant spontaneous urticaria and angioedema. Through retrospective application of the BSACI guidelines,⁷ indications for Pen-A testing were verified for each case.

Characterization of patients as per clinical history

A standardized pro-forma was employed to systematically capture relevant data from clinical records. To clinically determine the likelihood of Pen-A, we classified patients into 4 categories according to the details of symptomatology and temporal association (Table I).

The clinical history was classed as “likely type I HSR to penicillin” where there was rapid onset with symptoms including rash/urticaria, angioedema, bronchospasm, or hypotension within 1 hour of administration of the first dose. A “likely type IV HSR to penicillin” was deemed when patients described delayed onset symptoms (>1 hour after first dose or during a course of therapy).

Patients were classified as “HSR to penicillin unlikely” in the presence of symptoms that were not suggestive of an immunologically mediated reaction, and the absence of a temporal association or confirmed tolerance on subsequent exposure to the same drug. Finally, patients were grouped into an “indeterminate history” category if the reaction details or temporal association was ambiguous or unknown, or when there were significant gaps in the available information.

We performed reliability and validity assessment for this clinical classification at the initial phase of data collection. To check for any intraobserver variation, 20 randomly selected patients were classified on 2 separate occasions (1 week apart) by a single operator (OEM). After this, we also carried out an interobserver reproducibility validation on another 10 randomly selected cases by 3 experienced allergy specialists independently.

On the basis of our recent publication¹⁹ that describes a clinical decision support system (CDSS), we risk stratified patients (Table II) as “low risk” and “high risk” according to the clinical characterization of the index reaction, its severity, and presence or absence of associated cardiorespiratory comorbidity. Briefly, the

TABLE I. Clinical history of suspected penicillin allergy (basic prerequisite of a full history—temporal association and nature of symptoms; precise details of type of penicillin not required for this classification)

1. Likely type I hypersensitivity reaction to penicillin	2. Likely type IV hypersensitivity reaction to penicillin	3. Hypersensitivity reaction to penicillin unlikely	4. Indeterminate history
One or more of the following symptoms ≤ 1 h of administration of the first dose:	One or more of the following symptoms >1 h after exposure to penicillin (regardless of the number of doses):	- No temporal association between symptoms and exposure - Subsequent exposure to the same drug without a reaction - Symptoms not suggestive of an immune-mediated reaction (eg, headache, blurred vision, isolated GI symptoms, etc.)	- The temporal association between drug administration and onset of symptoms is vague/unknown - Vague history with no details (eg, childhood label of penicillin allergy) - Patient is uncertain whether onset of symptoms happened after the first dose or after more than 1 dose - Adverse reaction after administration of >1 medications simultaneously
- Cutaneous symptoms: urticaria, pruritus, flushing - Angioedema - Rhinitis or rhinoconjunctivitis - Bronchospasm (chest tightness, SOB, wheezing, cough, desaturation, cyanosis) - Hemodynamic instability (presyncope, syncope, loss of consciousness, arrhythmia, seizures, cardiac arrest)	- Delayed-onset cutaneous manifestations such as maculopapular rash, urticaria/angioedema, nonspecific rash, pruritus, flushing - Other systemic responses, eg, FDEs, DRESS, SJS/TEN, AGEP - Other rare systemic HSRs (type II or III): hemolysis, acute interstitial nephritis, vasculitis, etc.		

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms syndrome; FDE, fixed drug eruption; GI, gastrointestinal; HSR, hypersensitivity reaction; SJS, Steven Johnson syndrome; SOB, shortness of breathing; TEN, toxic epidermal necrolysis.

TABLE II. Risk stratification¹⁹ into 2 groups (high and low) was based on structured clinical history and associated comorbidities

Low risk	High risk*
- GIT[†] symptoms only “Benign” rash only (urticaria, exanthematous rash, angioedema) >1 h after first dose or during a course of therapy - Poorly described symptoms but not deemed serious (no systemic involvement, no hospitalization[‡] $\pm$ history of mild/moderate well-controlled asthma $\pm$ mild/moderate well-controlled COPD $\pm$ stable cardiac comorbidity) - Presyncope only (after oral dose) - Amoxicillin or co-amoxiclav has been prescribed and tolerated since the “index episode”	- Upper and/or lower airway symptoms “Benign” rash only (urticaria, exanthematous rash, angioedema) ≤ 1 h after first dose - Poorly described symptoms not deemed serious (no systemic involvement, no hospitalization[‡] but there is a history of severe asthma or brittle asthma or unstable asthma (mild, moderate, or severe) $\pm$ unstable COPD $\pm$ unstable cardiac comorbidity) - Anaphylaxis^{22,23} (defined as any one of the following): - Upper and/or lower airway symptoms and rash - Upper and/or lower airway symptoms and syncope or presyncope $\pm$ rash - Collapse (severe hypotension) - Upper and/or lower airway symptoms and GIT symptoms - Rash $\pm$ GIT symptoms $\pm$ upper and/or lower airway symptoms $\pm$ collapse or presyncope or syncope

Risk stratification was possible in 221 of a total number of 231 patients (adequate information was not available in 10 patients for risk stratification).

COPD, Chronic obstructive pulmonary disease; DRESS, drug reaction with eosinophilia and systemic symptoms syndrome; GIT, gastrointestinal tract; HSR, hypersensitivity reaction; SJS, Steven Johnson syndrome; TEN, toxic epidermal necrolysis.

*Patients with a history suggestive of serious systemic nonimmediate HSR (eg, SJS, TENs, erythema multiforme, DRESS syndrome, etc) would not be classified as “low risk” or “high risk” as per this model because they are not considered for Pen-A delabeling.

[†]Gastrointestinal tract.

[‡]Admission to emergency department.

CDSS is an electronic (e) application to help nonallergy specialist health care professionals take a systematic drug allergy history by employing an e-questionnaire. The responses to the e-questionnaire interface with an e-clinical algorithm. Specifically, details regarding comorbidities including asthma, chronic obstructive pulmonary

disease, and cardiac status are also captured. The CDSS also enables identification of patients with a history of serious nonimmediate systemic HSRs such as Steven Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms syndrome.

Statistical analysis

Descriptive analysis was used to describe patient characteristics and clinical profiles. Demographic and clinical characteristics were tested for significant associations with the final outcomes. Odds ratios were calculated from a univariate analysis of unadjusted binary data based on patients with a confirmed type I HSR versus delabeled patients (patients with non-type I HSR were excluded). A P value of $<.05$ was considered statistically significant. Statistical analysis was conducted using MedCalc software, version 17.9 (Ostend, Belgium).

The study protocol was reviewed by the research and development department in HEFT and was registered as an audit with the clinical governance unit in HEFT.

RESULTS

The study flow diagram is summarized in [Figure 1](#). A total of 231 adult patients were included in the analysis. Patients who were lost to follow-up, those with missing data, or who declined investigations or did not undergo a challenge procedure after allergy tests were excluded from the analysis. Patients investigated for Pen-A in the context of perioperative anaphylaxis were also excluded because the primary objective of the study was to characterize patients with a label of Pen-A.

Our cohort included 149 (64%) females and 82 (36%) males, with a mean age of 51.22 (standard deviation $\pm$ 18.07) years. There was no significant association between gender and the likelihood of developing type I HSR to penicillin (odds ratio [OR] = 0.92; P = .89). One hundred and three (45%) patients had a label of “multiple antibiotic allergy,” 92 (40%) had a label of Pen-A with a requirement of recurrent antibiotics, and 7 (3%) had an absolute indication for penicillins.

One hundred patients (43% of total) could recall the name of the culprit penicillin, whereas the remainder were unable to specify which penicillin was implicated in the index reaction. The leading culprit reported was amoxicillin in 65 patients, followed by co-amoxiclav in 18 patients, flucloxacillin in 13, and piperacillin in 4 patients.

Critical analysis of clinical presentations of Pen-A

A majority (78% [n = 180]) of patients reported cutaneous manifestations. Only 25 patients (11%) denied any skin involvement, and the remaining 26 patients (11%) had no recollection of the details of the index reaction. Other organ involvement reported were upper airways (9% [n = 22]), lower airways (9% [n = 22]), cardiovascular (5% [n = 12]), gastrointestinal (4% [n = 10]), and nonspecific symptoms (8% [n = 18]; eg, headache, aches/pains, etc). Ten patients (4%) presented with symptoms that met the World Allergy Organization criteria^{22,23} for anaphylaxis.

Using the clinical classification described in [Table I](#), 12% (n = 27) of patients reported symptoms of “likely type I HSR to penicillin,” 28% (n = 65) were “likely type IV HSR to penicillin,” 12% (n = 28) were classified as “hypersensitivity reaction to penicillin unlikely,” and 48% (n = 111) of patients were in the “indeterminate history” group.

Subgroup analysis of the 4 categories is summarized in [Figure 1](#). Of the 27 patients in the first group, type I HSR was confirmed in 7 (26%) cases by either skin testing or supervised challenge. Most of the patients in the “indeterminate history” group (91% [103/111]) had a negative penicillin challenge. One hundred percent of the “HSR unlikely” category had negative penicillin challenge and were successfully delabeled.

Organ involvement in confirmed type I HSR versus delabeled patients

Detailed characterization of presenting symptoms revealed notable differences between patients with proven type I HSR to penicillin and delabeled patients ([Figure 2](#)). The most common documented organ involvement in patients with confirmed type I HSR was skin (100%) followed by upper airways (36%), lower airways (28%), cardiovascular (21%), and gastrointestinal (7%) system. Eight of fourteen (57%) of those with confirmed Pen-A reported urticaria and/or angioedema, whereas the skin rash details were not documented in the remaining 6 patients. Six of 14 (43%) patients had documented anaphylaxis, whereas 8 patients reported cutaneous symptoms only.

According to the clinical history of the index reactions, patients who reported urticaria/angioedema (OR = 5.46; P = .003), respiratory symptoms (OR = 6.70; P = .002), and cardiovascular compromise (OR = 7.87; P = .006) are at a higher risk of immediate HSR to penicillin. In addition, anaphylaxis (OR = 30.60; P < .001) and admission to emergency department (OR = 7.08; P < .001) increased odds of type I HSR to penicillin significantly ([Table III](#)).

On the other hand, most of the delabeled patients presented with nonspecific skin rashes and only 42 (20%) patients described urticaria and/or angioedema. Notably, 36% of these 42 patients had a documented diagnosis of spontaneous urticaria and angioedema. Systemic symptoms were significantly less frequent in delabeled patients compared with cases with a confirmed type I HSR to penicillin. Furthermore, only 10% (21/209) of delabeled patients were admitted to the emergency department compared with 43% (6/14) of those with a confirmed Pen-A.

Risk stratification of patients

Based on the criteria in [Table II](#), subjects in our cohort were classified as being at “high risk” or “low risk.” One hundred and forty-three (62%) patients were classified as “low risk” and 78 (34%) as “high risk,” and relevant clinical details were not available in the remaining 10 patients (4%).

“Low risk” group. Our data showed that 94% (n = 134) of “low risk” patients were successfully delabeled. Of the remaining 9 patients (6%) in the “low risk” group, 3 (2%) were diagnosed with type I HSR and 6 (4%) with nonimmediate HSR. Importantly, 5 of these 9 patients had a supervised challenge and only developed a benign skin rash requiring treatment with oral antihistamines.

“High risk” group. A total of 83% (n = 65) of “high risk” patients were successfully delabeled. Eleven patients (14%) were diagnosed with type I HSR and 2 patients (3%) with type IV HSR.

Characterization of patients according to the final outcome ([Figure 1](#))

Patients with confirmed diagnosis of immediate (type I) HSR to penicillin (n = 14). Type I HSR to penicillin was confirmed in 14 patients (6%) in our cohort (none of them were classified under the “HSR to penicillin unlikely” group). Among these patients, 6 were diagnosed with a positive IDT, 3 had a positive SS IgE, and 5 patients had a positive supervised challenge. Fifty percent (n = 7) of these 14 patients

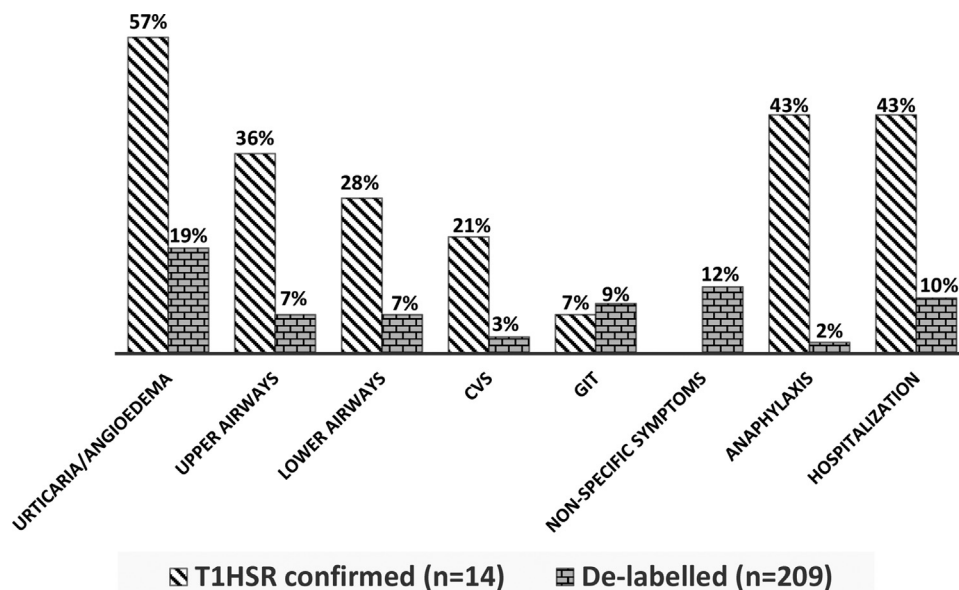


FIGURE 2. Breakdown of organ involvement and symptom severity in patients with confirmed type I hypersensitivity reaction (T1HSR) to penicillin compared with delabelled cases. CVS, cardiovascular system; GIT, gastrointestinal tract.

TABLE III. Odds ratios for clinical characteristics associated with Pen-A

Variable	Frequency in T1HSR (n = 14)	Frequency in delabelled patients (n = 209)	Odd ratio for having penicillin T1HSR	Significance (P value)
Female gender	9	138	0.93	NS
Male gender	5	71	1.1	NS
Anaphylaxis (WAO criteria)	6	5	30.6	<.001
Hospitalization	6	20	7.1	<.001
Time elapsed since index episode ≤ 5 y	8	63	3.1	.04
Time elapsed since index episode >5 y	6	146	0.32	.04*
Skin involvement	14	158 (26 unknown)	4.7	NS
CSUA	2	29	1.0	NS
Classification as high risk	11	65 (10 unknown)	7.6	.003
Classification as low risk	3	134 (10 unknown)	0.13	.002†
Variable	Odds ratio for being delabeled		Significance (P value)	
Time elapsed since index episode >5 y	6	146	3.1	.04
Classification as low risk	3	134 (10 unknown)	3.0	.02

Odds ratios were calculated from univariate analysis of unadjusted, binary data based on patients with confirmed type I HSR versus delabelled patients (patients with non-type I HSR excluded). Total patient number = 223.

CSUA, Chronic spontaneous urticaria and angioedema; Pen-A, penicillin allergy; T1HSR, type I hypersensitivity reaction; WAO, World Allergy Organization.

*Patients with time elapse >5 y have lower odds of having T1HSR to penicillin—3 times less likely. On the reverse, these patients have a high likelihood of being delabelled for penicillin allergy.

†Patients in the “low risk” group have significantly lower odds for having T1HSR to penicillin. On the reverse these patients have a high likelihood of being delabelled for penicillin allergy.

presented with a history suggestive of type I HSR, and the remaining 7 patients presented with an “indeterminate history” (n = 6) and a history of “likely type IV HSR” (n = 1).

Eleven of the 14 cases (79%) were stratified as “high risk” as per Table II. Application of the risk stratification module (Table II) in these 14 cases, the majority (79% [n = 11]) were categorized as “high risk.”

Two of the 3 patients with a positive SSiGE reported a history suggestive of type I HSR to penicillin. One of these patients had a positive SSiGE to amoxicillin, and the other patient was positive

to amoxicillin and penicillin V. SSiGE was positive to amoxicillin, penicillin V, and penicillin G in the third patient whose index reaction was classified as “indeterminate.” Although these results may have been false positive, after a risk-benefit analysis, a cautious approach was taken in view of the concomitant chronic respiratory illness in this patient.

Patients with confirmed nonimmediate (type IV) hypersensitivity reaction to penicillin (n = 8). All 8 patients were in the “low risk” group and presented with benign

skin rashes only without systemic symptoms. Six of the 8 patients developed a delayed, benign cutaneous reaction after an oral penicillin challenge. The remaining 2 patients developed erythema and induration at the IDT sites that correlated temporally with their index reaction. The first patient developed a positive delayed IDT to amoxicillin 48 to 72 hours after the procedure. Similarly, the second patient developed a positive IDT to MDM approximately 24 hours later. In both cases, IDT results were in keeping with the index reaction. On that basis, type IV HSR was confirmed in these 2 cases and an oral challenge was deemed clinically unsafe.

Delabeled patients (n = 209). The majority of our cohort ([209/231], 90%) had a negative penicillin challenge and were safely delabeled from Pen-A. Only 18 (9%) of delabeled cases presented initially with urticaria. Notably, 5 (28%) of these 18 patients had an underlying diagnosis of spontaneous urticaria and angioedema that may explain the inaccurate label of Pen-A.

Penicillin skin testing was found to have a negative predictive value (NPV) of 97.6% and 97.2% for immediate and non-immediate HSR, respectively.

DISCUSSION

This study involved a careful and critical characterization and risk stratification of patients who underwent allergy workup for Pen-A. The risk stratification was aligned to the clinical algorithm used in the CDSS.¹⁹ Our data showed that 100% of patients where Pen-A was deemed unlikely on the basis of clinical history were safely delabeled employing standard allergy investigations. Similarly, a high proportion (93%) of cases in the indeterminate category and those where the clinical history was suggestive of a nonimmediate reaction (91%) were also delabeled. The NPV of the criteria used to classify patients into the “low risk” category was high at 94%, and the odds of developing type I HSR was significantly less in this group of patients (OR = 0.13; $P = .003$). The NPV of skin tests for an immediate and nonimmediate HSR was >95% and in keeping with previous studies (a high NPV between 90% and 100%).^{3,4,24}

The most common clinical category based on the clinical characterization of the index episode in our cohort was “indeterminate” (48%) followed by those with a clinical history of nonimmediate HSR (28%) and those where Pen-A was deemed unlikely (12%). A high proportion of patients in these categories were successfully delabeled. Specifically, we carefully mapped the clinical presentations of all the cases with the risk stratification model applied to the CDSS (Table II) described recently¹⁹ and found a very high NPV for those classified as “low risk.” Our data provide proof of concept to apply the CDSS in routine clinical practice in the UK NHS as a means to mitigate the adverse impact of spurious Pen-A label and reduce health care costs. However, this approach requires rigorous prospective validation in a multicenter study before it is introduced in routine clinical practice. In a previous study, involving 102 randomly selected hospitalized patients with a label of Pen-A, we reported that at least 40% were suitable for a direct penicillin challenge without the need for allergy tests.²⁵ A recent North American study showed that a guideline-based direct penicillin challenge (without prior allergy tests) enhanced safe prescription of penicillin by approximately 2-fold amongst inpatients with a label of “Pen-A” (without a significant increase in adverse reactions compared with standard of care).¹⁶ The health economic

cost of spurious Pen-A has been estimated to be of the order of \$64 million USD in a cohort of 51,582 patients over a 3-year period in Southern California, USA.^{1,10} Implementation of a computerized guideline in the Harvard group of hospitals alone with 133,439 annual admissions has been estimated to produce cost savings of \$8.9 to \$13.7 million USD in the first year.¹¹

Our data suggest that the time elapsed since the index reaction is an important variable to be factored into the delabeling process. This is particularly relevant in the context of type I HSR because previous studies have highlighted loss of sensitization or decline in the rate of sensitization after 5 years following the last exposure to penicillin.²⁶ Our data showed that 64% of the “true” Pen-A patients had their index reaction within the previous 5 years. In contrast, the odds of a type I HSR was significantly less in patients who had an interval of more than 5 years since the index reaction (OR = 0.32; $P = .04$). This suggests that the longer the gap between the index reaction and the allergy tests, the greater the likelihood of excluding Pen-A. However, this should be assessed in conjunction with the clinical presentation and other clinical variables.

We found that chronic spontaneous urticaria and angioedema (CSUA) can be an important confounder during the evaluation of suspected Pen-A. In our cohort, a history of CSUA was present in 26% of false-positive cases that presented with “history of likely type I HSR to penicillin” and in 23% of false-positive cases with a “history of likely type IV HSR to penicillin.” The estimated prevalence of CSUA in the general population ranges from 0.5% to 5%^{27,28}; it is plausible that infection-triggered urticaria in these patients may have been misinterpreted as Pen-A.

A recent study from France described a prediction model for beta-lactam allergy.²⁹ They employed 2 different methods including multivariate logistic regression and a “decision tree” on a large cohort of patients who had previously undergone Pen-A tests. They chose 9 candidate variables and related to the final outcome (positive skin test or drug challenge) and identified the following variables: signs and symptoms (in particular history of anaphylaxis), years elapsed since reaction, temporal association of symptoms (chronology), age at the time of reaction, and number of reactions per patient as important predictors. They reported an NPV of 82%. They also applied this model in a prospective study involving 200 patients and reported a similar NPV. Their cohort, however, included 21% of patients with a previous history of anaphylaxis. This proportion is much higher in comparison with the cohort in this study (4%) and those reported by others (3.1% to 12%).^{5,17,30}

The current study has limitations. First, it is a single-center retrospective analysis. Secondly, this is a relatively small cohort. Thirdly, we carried out a retrospective data extraction and analysis. However, our center has a highly systematic method of drug allergy history evaluation and adheres to the BSACI and EAACI guidelines for the investigation and management of type I (immediate) and type IV (nonimmediate) HSR to penicillin. The clinical classification (Table I) used in this study was validated between 3 experienced allergy specialists with respect to interoperator variability, and all the data were gathered by a single clinician in a standardized format. Fourthly, recall bias should be considered, especially when a long time lapsed from the index reaction to Pen-A testing. Fifthly, our cohort is influenced by selection bias and may not be representative of all cases of Pen-A in the community because family physicians and specialist referrals usually involve patients with a diagnostic label

of Pen-A in the context of an infection-related comorbidity (eg, recurrent infections, immunodeficiency, asplenia/hyposplenism, "multiple antibiotic allergy," etc). Furthermore, those with a clear history of recent penicillin-induced anaphylaxis and/or recurrent penicillin-induced anaphylaxis are usually given a clinical diagnosis without undertaking Pen-A tests (with occasional exceptions). Sixthly, 26% of cases (of 312) identified in the database search were excluded from analysis for reasons stated in Figure 1. Finally, patients with an indeterminate clinical history and a positive skin test and/or SSiGE were not subjected to a challenge procedure after a risk-benefit analysis. In particular, cases with an isolated positive SSiGE test may have been false positive (poor positive predictive value of SSiGE to penicillin has been reported previously³¹).

Our data supported the potential application of a computerized guideline-based approach in the UK NHS as a means to rapidly and safely delabel "low risk" patients carrying a label of Pen-A. There is a high and unmet demand for allergy services in the United Kingdom,⁸ and antimicrobial resistance is currently on the national risk register.³² Specialist centers undertake Pen-A testing on an elective basis with the aim of delabeling patients, and this service is not routinely available for inpatients and in an acute setting. Therefore, there is an urgent need for a rapid mechanism for a nonallergy specialist across multiple disciplines to identify patients most unlikely to be "truly allergic" (ie, "low risk"), and the CDSS tool provides an excellent opportunity in the triaging process. This, however, requires prospective and rigorous validation in a multicenter study before its application in routine UK clinical practice.

In conclusion, careful clinical characterization and risk stratification of patients is key to patient selection in successful Pen-A delabeling. Patients classified as "low risk" as per our clinical algorithm seem most suitable candidates for a direct supervised graded challenge in a controlled clinical environment. These data provide "proof of concept" for direct administration of penicillins in "low risk" patients for rapid delabeling. A multicenter study for testing feasibility of this approach and clinical validation is needed.

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