Alnæs et al. World Allergy Organization Journal (2023) 16:100829
http://doi.org/10.1016/j.waojou.2023.100829

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

A new pathway for penicillin delabeling in Norway

Marie Bjørbak Alnæs, MD[a,b]*, Oddvar Oppegaard, PhD[c,b], Bård Reiakvam Kittang, PhD[b,d,e], Stein Håkon Låstad Lygre, PhD[a], Anine Bernhoft Langeland, CNS[c], Brita Skodvin, PhD[f], Tormod Bjånes, PhD[g] and Torgeir Storaas, PhD[a]

ABSTRACT

Background: Penicillin allergy is self-reported by 3–10% of patients admitted to hospital. The label is wrong in 90% of the cases and has severe health implications. Penicillin-delabeling can reverse the negative effects of the label, and pathways adapted to local practice are needed. No tools are available in Norway for penicillin delabeling outside an allergy clinic.

Objective: To create and validate the first penicillin delabeling pathway applicable outside an allergy clinic in Norway.

Methods: An interdisciplinary taskforce created a penicillin allergy delabeling program (PAD) adapted to the Norwegian health care system. This was validated in a prospective, single-center study. Very low-risk and low-risk patients underwent a direct oral penicillin challenge and high-risk patients were referred for allergologic evaluation.

Results: One-hundred forty-nine patients declaring penicillin allergy were included. Seventy-four (50%) were very-low- and low risk patients suitable for a direct oral penicillin challenge resulting in only 1 mild reaction. Sixty high-risk patients were eligible for an oral penicillin challenge after allergologic evaluation; 3 patients reacted non-severely.

Conclusion: We have created and demonstrated feasibility of the first penicillin delabeling program (PAD) applicable in a hospital setting outside an allergy clinic in Norway. Our data suggest this is safe and beneficial, with 49% patients delabeled through a direct oral penicillin challenge, performed without any serious adverse events, and an overall 87% delabeling rate.

Keywords: Critical pathway, Drug hypersensitivity, Penicillins

INTRODUCTION

Betalactam antibiotics represent the cornerstone of most guidelines for treatment of infectious diseases, both in primary care and hospitals.[1] The narrow spectrum betalactam, penicillin, remains the drug of choice in the majority of clinical settings in the Nordic countries, due to its well-established clinical efficacy combined with a favorable ecological profile. However, up to 10% of all patients admitted to hospital report penicillin allergy or have penicillin allergy registered in their

[a]Section of Clinical Allergy, Department of Occupational Medicine, Haukeland University Hospital, 5020 Bergen, Norway
*Corresponding author. Helse Bergen, 5021 Bergen, Norway. E-mail: marie.bjorbak.alnes@helse-bergen.no
Full list of author information is available at the end of the article
http://doi.org/10.1016/j.waojou.2023.100829

Received 4 July 2023; Received in revised from 21 September 2023; Accepted 22 September 2023
Online publication date 16 October 2023
1939-4551/© 2023 The Author(s). Published by Elsevier Inc. on behalf of World Allergy Organization. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

medical records.[2] Due to potential cross-reactivity between penicillin and other betalactam-antibiotics, the label "penicillin allergy" necessitates administration of second- or third-line antibiotics, which is associated with an increased risk of adverse events and up to a 14% rise in mortality.[3] Moreover, it is associated with extensive health economic implications, including prolonged stays in hospital, increased nosocomial infection rates, higher costs of treatment, and stronger selection pressure for antibiotic resistance.[4]

The penicillin allergy label is found to be incorrect in 9 out of 10 people.[5] Re-evaluating penicillin allergy labels, therefore, would allow large numbers of patients to receive appropriate first-line antibiotics when needed. Furthermore, a pro-active delabeling strategy might lead to a significant reduction in the use of broad-spectrum antibiotics, reducing selection pressure for antimicrobial resistance.[4] In line with this, investigation and delabeling of penicillin allergy is regarded as an essential part of any international antibiotic stewardship program and a highlighted measure to combat antibiotic resistance.[6,7] Norwegian guidelines[8] have not yet addressed penicillin allergy delabeling. This might be due to the lack of validated diagnostic tools and poor access to allergy specialists in Norway. The gold standard for evaluating penicillin allergy is a comprehensive investigation consisting of a detailed allergy history, skin testing and, where appropriate, a drug challenge.[9] The resources and allergy expertise for this pathway are scarce and represent a major barrier. A simplified procedure for investigating penicillin allergy in low-risk patients could potentially be performed by the medical staff in hospital wards. However, a validated algorithm for stratifying patients into high- and low-risk categories is not currently available in Norway. Our aim was to design and validate the first penicillin allergy-delabeling (PAD) program applicable in a Norwegian hospital setting outside an allergy clinic.

METHODS

Study design and study population

The study consists of 3 parts: Construction of a clinical pathway, a retrospective case-report study, and a prospective clinical single center pilot study. The study was performed at Haukeland University Hospital (HUH), Norway between March 2021 and March 2022. HUH is a tertiary care facility serving a catchment area of approximately 450 000 inhabitants and with a specialist allergy service. Participants were recruited among patients at HUH admitted to the Infectious Diseases ward or referred to the allergy outpatient clinic. Patients aged $\geq$18 years with self-reported penicillin allergy, or with penicillin allergy registered in their medical records, were eligible for inclusion. Critically ill patients and patients with respiratory and/or hemodynamic instability were excluded.

Development of the penicillin-allergy delabeling program

In line with published recommendations for developing clinical tools,[10–12] we established an interdisciplinary group of senior physicians, junior doctors, specialist nurses, and patients recruited from HUH's patient representative program. The doctors and nurses all work at the Section for Infectious Medicine, Internal Medicine, or Allergology Department. We performed an unstructured literature search for penicillin-delabeling programs, including both pilot studies and validated programs. Using a consensus-based process starting with a nominal group[13] and further an adapted Delphi method[14] until consensus was reached for a pilot version, we developed a pathway for delabeling penicillin-allergy, adapted to the Norwegian health system applicable for a hospital setting, outside an allergy clinic.

Validity

The items in the pathway were evaluated by the interdisciplinary group to assess understandability, feasibility, and safety, and to ensure adherence to current best practice. Nine case stories based on real patients previously assessed at the allergy outpatient clinic including specific IgE-measurements, skin testing, and where appropriate, a penicillin challenge, were selected (Supplement 1). These cases were anonymized and underwent internal validation by the physicians in the consensus group. The cases covered all risk stratification groups and were forwarded to 50 physicians in the Western Norway Health

Region working in all fields of practice, such as internal medicine (with all subspecialties), surgery (with all subspecialties), anesthesiology, otorhinolaryngology, gynecology, emergency medicine, family medicine, allergology, and orthopedics, for risk stratification as an external validation. Two specialists in Allery and Clinical Immunology participated; the other respondents were clinicians in the hospitals' other departments. In the evaluation, errors were classified as non-severe if the physician classified the patient in a higher risk stratification group as the correct answer, and severe if the patient was classified in a lower risk stratification group as deemed correct.

Reliability

To examine reliability of the risk stratification form, all patients included in the prospective study pilot were risk stratified twice: on their primary contact with the hospital and again 4–8 weeks later. The second evaluation was performed as a phone interview by the corresponding author for low- and very low-risk patients and for high-risk patients by a physician at their appointment at the allergologic clinic. All patients were restratified by an allergologist.

Penicillin challenges

Patients risk stratified as very low- and low-risk underwent a direct, non-graded oral penicillin challenge. This was performed at the infectious diseases ward or at the outpatient allergy clinic. All engaged personnel were educated towards penicillin allergy, delabeling, and anaphylaxis, including the use of adrenaline auto-injectors. If the index penicillin was known, it would be used for the challenge. If not, a single dose of 500 mg amoxicillin was administered. All high-risk patients deemed eligible for a penicillin challenge underwent a titrated penicillin challenge in the outpatient allergy clinic, but only after a full allergologic work up, adhering to the current standards for evaluation of penicillin allergy.[15-17] The titrated challenge started with 25% of a full therapeutic dose of the index penicillin (or 125 mg amoxicillin), followed by a full therapeutic dose of the index penicillin (or 500 mg amoxicillin) if they did not react to the first dose after 30 min. The dosing was chosen to follow already established official hospital protocols for penicillin challenges. The patient flow is demonstrated in Fig. 1.

Skin testing

High-risk patients underwent skin prick and intradermal testing at the allergy outpatient clinic. Very low- and low-risk patients that consented to further testing had skin tests performed at the allergy clinic on a later appointment. Patients were tested for the index penicillin, penicillin G, penicillin V, amoxicillin, and ampicillin. All tests were diluted in line with recommendations from the European Academy of Allergology and Immunology (EAACI).[16] Patients were instructed to report delayed skin reactions from the intradermal testing and were handed out a standardized form to report such late reactions.

Laboratory methods

The following parameters were measured in all high-risk patients and consenting very low- and low-risk patients. Serum specific IgE measurements were performed using ImmunoCAP method (Thermo Fisher Scientific, Uppsala, Sweden). Total IgE was measured using a reference value of 2.0–

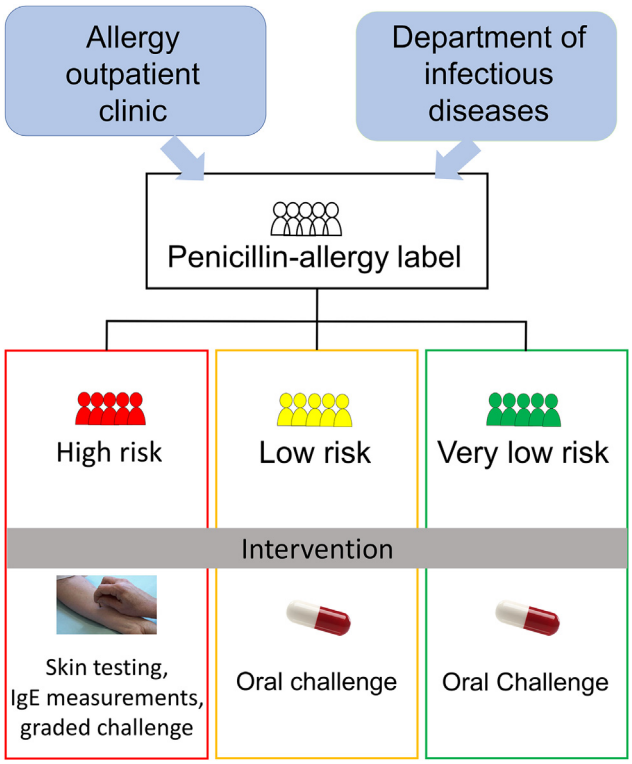

Fig. 1 Patient flow.

297 kU/L. Serum specific IgE-Penicilloyl G (c1), Ig E-Penicilloyl V (c2), IgE- Ampicilloyl (c5), IgE- Amoxicilloyl (c6) and IgE-Cefaclor (c7) were measured, all with an upper value for normal of <0,35 kU/L.

Statistics

All analyses were performed with IBM©SPSS© Statistics, Version 29, datasets. Descriptive statistics were applied to demographic data. In order to examine reliability of the risk stratification form, we performed Cohen's kappa test for the measurement of agreement.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics Western Norway (REK-West: 199210), listed at Clinical Trials gov. and all patients provided informed, written consent.

RESULTS

The pathway

We developed a pathway compromising 3 items:

1. Risk stratification tool (supplement 2) to be used by a physician when the patient was admitted to hospital or as soon as the patient was eligible for screening.
2. Drug challenge proforma (supplement 3), detailing the process for the penicillin challenge test.
3. Standardized phrases (supplement 4) for communicating the result of the penicillin challenge to the patient and health care givers, with a reminder to update all electronic health records.

The risk stratification tool allows the physician to stratify the patients into the following 3 groups:

1. Very-low risk of a penicillin allergy: Directly delabeled†[1]
2. Low risk of a penicillin allergy: A direct oral penicillin challenge can be performed.
3. High risk of a penicillin allergy: Refer the patient to an allergy clinic for evaluation.†

The patients were risk stratified into very-low, low- or high-risk of penicillin allergy through clinical criteria in the risk stratification form (supplement 2). All forms were created as text that could be implemented using "copy-paste" in all software solutions as free share phrases and be printed for use as paper versions. All forms were translated into English and available as supplement 2-4.

Validity

We distributed 9 clinical cases with the risk stratification form to 50 physicians of all levels of experience and all fields of clinical practice in the participating local, regional, and university hospitals of Western Norway. We received 42 answers and detected 2 severe errors repeatedly in the replies: A pregnant patient case was graded in line with her allergic reaction (non-severe skin reaction) ignoring the pregnancy by 10 respondents, and common words used by patients for urticaria led 8 respondents to classify urticaria as low-risk exanthemas. Isolated gastrointestinal symptoms were classified as low- or high-risk instead of very low risk by 15 respondents, causing a non-severe error. No other repeated errors were found, but 1 respondent graded the anaphylaxis case as low risk, a very severe error. The answers led us to perform a repeated consensus round: Here wording of items was changed, and a warning stating that pregnant patients are high-risk and should always be referred to an allergology clinic added. After subsequent assessment, repeated validation was performed and amended forms were distributed to 40 new physicians. No severe errors were detected in the 33 responses obtained. The tendency to rate very low risk patients as low risk (non-severe error) stayed but will not lead to dangerous clinical implications. The 75 responders were well distributed across all levels of experience and gender, but a high percentage (59%) worked in a hospital with an allergology service, and 57% worked in an internal medicine department. Physicians working in the field of otorhinolaryngology, gynecology, emergency

[1] In the study, a direct oral penicillin challenge was performed also for very-low risk patients, for validation purposes.

	n	(%)
Level of experience[a]		
Junior doctor	37	(49%)
Senior doctor	38	(51%)
Male gender	40	(53%)
Access to allergologic service	44	(59%)
Field of practice		
Internal medicine	43	(57%)
Surgical specialties	16	(21%)
Anesthesiology	5	(7%)
Other	11	(15%)
Total	75	(100%)

Table 1. Demographics of the physician validation survey. [a]*Doctors were classified as senior if they were board registered specialists*

medicine, family medicine, allergology, and orthopedics are summarized as "others" in Table 1. We found no significant differences in the answers between the groups.

Risk stratification and validation

A total of 149 patients labelled as penicillin allergic were included in the study. The patient characteristics are listed in Table 2.

The history of the index reaction to penicillin was most commonly urticaria (n = 57, 38%). Other reactions comprised maculopapular exanthemas (MPE) (n = 45, 30%); unknown reaction >10 years ago (n = 28, 18%); anaphylaxis (n = 18, 12%); and hospital admission for severe reaction (n = 18, 12%). 222 symptoms among 149 patients were recorded. For 84 patients, more than 1 symptom from the risk stratification score was found and 69 patients stated only one symptom. Among the 149 patients included, 16 (11%), 58 (39%), and 75 (50%) were categorized as very low-, low- and high-risk individuals, respectively.

	n	Percent
Total of patients	149	100%
Mean age	47.7	
Age range	18–92	
Female patients	92	62%
White patients	140	94%
Other ethnicity	9	6%

Table 2. Demographics of the study population

Penicillin challenge

All 16 very-low risk patients underwent an uneventful direct penicillin challenge.

In the low-risk group 58 patients underwent a direct penicillin challenge. Here, 1 patient (1/58 = 2%) developed an MPE, 48 h after the challenge. It was a mild self-limiting reaction; no treatment was initiated. The remaining 57 low risk patients were delabeled uneventfully. A total of 75 high-risk patients were referred to the allergy outpatient clinic. Of these, 15 had a documented severe delayed index reaction (drug reaction with eosinophilia and systemic symptoms (DRESS) or severe cutaneous adverse reactions [SCAR]), or a documented anaphylaxis correlating with positive skin testing and/or detection of specific Immunoglobin E (IgE) towards penicillins. None of these patients underwent a penicillin challenge. The remaining 60 high-risk patients underwent a titrated penicillin challenge. In this group, 1 patient reacted to the penicillin challenge with a late onset (>6 h) urticarial rash, and 2 patients reacted with a dose-dependent immediate itch (3/60 = 5%). These all had negative skin testing and negative specific IgE's. Overall, a direct oral penicillin challenge delabeled 73 patients (49%). In total, 130 patients (87%) were delabeled.

Specific IgE measurements, skin testing

We aimed to examine all patients included with specific IgE measurements and skin testing. However, many patients with a negative penicillin challenge were not motivated for further skin testing, resulting in missing data for 14 patients (5 very-low risk and 9 low risk). All high-risk patients underwent skin testing and specific IgE measurements. Out of the total 135 patients who underwent skin prick and intradermal testing, 8/75 (11%) high-risk patients tested positive for specific IgE. One of the 16 patients in the very low-risk group had a positive skin test, but a negative penicillin

challenge. The remaining 126 skin tests were negative. Specific IgE measurements in serum were performed in 141 of the patients. Positive specific IgE measurements of either IgE- Penicilloyl G, IgE-Penicilloyl V, IgE-Ampicilloyl or IgE- Amoxicilloyl in serum was found in 8/75 (11%) of the patients in the high-risk group and 1 patient in the low-risk group. The missing 8 measurements were 5 very low- and 3 low-risk patients who had undergone a negative penicillin challenge. Three patients (2 high-risk-and 1 low-risk) with a positive specific IgE (but negative skin testing) towards penicillins, underwent a negative penicillin challenge. Six high-risk patients with positive IgE towards penicillin had experienced repeated anaphylaxis related to penicillin and were not challenged, but notably only 4 of these demonstrated positive skin testing (*Test results*, Table 3).

Restratification

Within the allocated time frame, 8 (5%) patients could not be reached for restratification. Two different physicians stratified 123 patients (83%). The remaining 18 (12%) patients were risk stratified by the same physician twice, creating a confirmation bias. We performed a Cohen's kappa test for measure of agreement to examine reliability of the risk stratification form, comparing the results from stratification of the patients and the restratification. The Cohen's kappa test showed a value of 0.89.

DISCUSSION

We have developed and validated the first risk stratification based PAD outside an allergy clinic in Norway. The overall delabeling rate was 87%, and 49% of the patients could be delabeled directly with an oral untitrated penicillin challenge, sparing the patient and the health system of resource-intensive allergologic examinations. The risk stratification proved safe. There were no reactions in the very-low risk group, and only one mild reaction in the low-risk group. In the high-risk group, 15 patients were not eligible for testing, and 3 patients reacted to the oral challenge even after negative skin testing and negative specific IgE measurements. We calculated a Cohen's kappa value of 0,89, demonstrating excellent reliability of the PAD. All together this demonstrates the PAD to be safe and with a good predictive value for real penicillin allergy.

As recommended in the process of developing new clinical tools[10–12] we established an interdisciplinary group to create the pathway. PADs have successfully been implemented in other countries[18,19] by similar approaches. Furthermore, a pilot study showing the feasibility of delabeling in Norwegian hospitals has been published.[2] There has been an emphasis on developing PADs adapted to the country and health system the pathways are developed for,[20] and a proactive approach has been recommended.[21] The most comparable health care system and prescription practice to Norwegian conditions are the Danish recommendations for penicillin allergy.[22] However, the nurses in our group reported a need for more explicit instructions for the penicillin challenge to feel safe to perform testing. We decided to construct a PAD in Norwegian, enabling us to adapt the pathway according to domestic clinical practice. Nevertheless, our program is based on the framework of other penicillin delabeling programs.[18,19,22] In Norway, nurses regularly discover drug allergy labelling and suspects adverse drug reactions.[23] In addition, they administer drugs on an everyday basis, and

	High risk	Low risk	Very low risk
n	75	58	16
Positive provocation test	3/60 (5%)	1/58 (2%)	0/16
Positive specific IgE in serum	8/75 (11%)	1/55 (2%)	0/11
Positive skint test[b]	8/75 (11%)	0/49	1/11 (9%)
Not challenged	15/75 (20%)	NA	NA

Table 3. Test results. [b]*Only four of the patients with a positive IgE towards penicillin also demonstrated positive skin testing*

perform penicillin challenges when indicated. Hence, it was crucial to include nurses in our interdisciplinary group. Clinical pharmacists are scarcely available in Norwegian hospitals and therefore not included in the procedure. However, we acknowledge the crucial role of the pharmacist in antibiotic stewardship[24,25] and a clinical pharmacologist advised the group. Including patients in the whole process enabled us to create a pathway with forms and procedures understandable to the patients. It also ensured that the pathway feels safe, relevant, and feasible to the patients. We believe that the input from patients throughout improved outcomes and uptake rates.

Norway has a highly digitalized public health system, but as in many other countries, most software solutions do not communicate drug allergy labelling between them. Most hospital computers are stationary and laptops are often not allowed in patient rooms. We therefore focused on developing user-friendly forms with simple text, that would perform just as well on paper as on screen. We also created standardized conclusion phrases as the task of spreading and sustaining drug allergy labelling, and delabeling, is a known challenge.[26,27] Education of patients and personnel is a key component in delabeling programs, as it has shown to be a success factor towards increasing delabeling rates and prevent subsequent relabeling.[28] We believe that the educational aspects of our study improved patient uptake rates.

The validation of the risk stratification form as a retrospective case study was performed twice, as the first validation detected 2 severe errors repeatedly in the replies. After improving the form renewed validation was performed. No severe errors occurred in the second round. We demonstrated good internal consistency, high inter-item relatability and safe application of the improved risk stratification form. Still, in line with other publications,[29] a classification error can always occur, and participating clinicians must be educated towards detecting and treating drug challenge reactions. Norway has very few specialists in Allergology; 2 of the authors constructing the study are such specialists, but due to the scarcity of allergologists we did not perform a separate validation of the form with specialist in Allergology.

Our clinical pilot study design was pragmatic and included unsorted patients presenting at the hospital with an additional penicillin allergy labelling. We performed a Cohen's kappa test for measure of agreement to examine reliability of the risk stratification form, comparing the results from stratification of the patients and the re-stratification. The Cohen's kappa test showed a value of 0.89. A Kappa value of 0.81–1.00 is considered excellent agreement.[30] The agreement was not 1.00, as 3 cases were risk stratified to a lower risk category (from low-to very-low-risk) at restratification. These patients all suffered solely gastrointestinal side effects from penicillin. The test confirms excellent repeatability in the form of internal consistency, test-retest reliability, and inter-rater reliability.

We found a greater percentage of patients suitable for a direct oral penicillin challenge compared to an Australian group,[18] but in line with a study from the Netherlands.[24] We found that a single dose penicillin challenge for very low- and low risk patients facilitated appropriate antibiotic prescribing (data not shown), which in Norway typically includes a penicillin.[31] Our patient population had an overrepresentation of females, correlating with female sex as a known risk factor for reported penicillin allergy,[32] and the ethnicity distribution corresponds with Norwegian demographics.[33] This suggests that the PAD has been tested in a representable and generalizable population. Norway has a homogenic public health system and as our hospital serves a whole health region, we suggest that the findings are transferable to further Norwegian health regions and probably to other Northern European countries, as results are in line with earlier reported prevalence of penicillin allergy in Europe.[34,35] We therefore consider the external validity to be sufficient.

In the high-risk group, most patients reported isolated urticaria. Only 1 of these patients reacted to the oral penicillin challenge, developing urticaria >6 h afterwards. Urticaria may occur in true penicillin allergy and is seen as part of immediate allergic reactions including anaphylaxis. Earlier studies[36] have shown that the time interval between penicillin administration and development of urticaria is significant. However, most patients have poor recall of this timing and

may confuse urticaria with other exanthemas. In everyday clinical practice, the experience of the physician and nurses performing the risk stratification also varies widely. For safety reasons, we therefore believe it is important for urticaria to remain an exclusion criterion for a direct penicillin challenge.

Our study has some limitations. Initial validation was performed prospectively only by few physicians, with subsequent validation work of the risk stratification form conducted retrospectively as a case study. In addition, the sample size was small. We did not perform prolonged penicillin challenges, despite Danish data suggesting that prolonged penicillin challenges increase the rates of positive challenges, especially in delayed reactions,[37] as later guidelines advice against it.[21] Lastly, we did not re-check specific IgE or repeat skin testing in high-risk patients with a negative penicillin challenge and previous negative specific IgE due to the pragmatic design of the study, the limited resources for allergy testing and the ongoing discourse of the necessity of retesting patients after tolerating a penicillin challenge.[38,39]

We have demonstrated excellent safety, validity, repeatability, and feasibility of Norway's first non-allergist delivered penicillin allergy delabeling pathway. Our multidisciplinary approach was key to its success and is expected to motivate further implementation of the delabeling program. Furthermore, the pathway developed in the project may be implemented in all other hospitals across the country, underpinned by the fact that it is about to be included in the Norwegian national guidelines for the use of antibiotics in a hospital setting. This will aid and improve antibiotic stewardship for patients with declared penicillin allergy, decreasing the risk of developing antibiotic resistance.

Abbreviations

PAD, Penicillin delabeling program; IgE, Immunoglobin E; REK-West, The Regional Committee for Medical Research Ethics Western Norway; MPE, Maculopapulous exanthema; DRESS, Drug reaction with eosinophilia and systemic symptoms; SCAR, Severe cutaneous adverse reactions.

Acknowledgements

We would like to thank specialist nurses Marianne Sævik and Hanne Søyland for facilitating the provocation testing at the Infectious medicine department.

Funding

The Research Project was sponsored by a PhD grant from The Norwegian Western health region, research grants from The Norwegian Asthma and Allergy association, the Norwegian association for allergology and clinical immunology and the Norwegian association of Otorhinolaryngology and Head-and neck surgery (no grants numbers applies). The funding sources had no involvement in any parts of the study or publication.

Availability of data and materials

The datasets used are available from the corresponding author on reasonable request.

Author contribution

Marie Alnæs, Study design, writing the manuscript, patient recruitment, conduction of telephone interviews, challenge tests and data analysis. Torgeir Storaas, Study design, writing the manuscript, patient recruitment, challenge tests. Oddvar Oppegaard, Study design, writing the manuscript, patient recruitment, challenge tests. Bård Reiakvam Kittang, Study design, writing the manuscript. Stein Håkon Låstad Lygre, Study design, data analysis, statistician. Anine Berhoft Langeland, Study design, patient recruitment, challenge tests. Brita Skodvin, Study design, writing the manuscript. Tormod Bjånes, Study design, writing the manuscript.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics Western Norway (REK-West: 199210), listed at Clinical Trials gov. and all patients provided informed, written consent. No AI tools were used to perform or write this work.

Competing interest

All authors consent the material for publication. The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100829.

Author details

[a]Section of Clinical Allergy, Department of Occupational Medicine, Haukeland University Hospital, 5020 Bergen, Norway. [b]Department of Clinical Medicine, University of Bergen, 5021 Bergen, Norway. [c]Department of Medicine, Haukeland University Hospital, 5020 Bergen, Norway. [d]Haraldsplass Deaconess Hospital 5009 Bergen, Norway. [e]Department of Nursing Home Medicine, 5145 Fyllingsdalen, Norway. [f]The Norwegian Advisory Unit for Antibiotic Use in Hospitals, 5020 Bergen, Norway. [g]Department of Medical Biochemistry and Pharmacology (MBF) Haukeland University Hospital, 5020 Bergen, Norway.

REFERENCES

1. Norwegian guidelines for the use of antibiotics https://www.antibiotika.no/.

2. Steenvoorden L, Bjoernestad EO, Kvesetmoen TA, Gulsvik AK. De-labelling penicillin allergy in acutely hospitalized patients: a pilot study. *BMC Infect Dis*. 2021;21(1):1083.
3. Kimberly Md Mea Blumenthal. Recorded penicillin allergy and risk of mortality: a population-based matched cohort study. *J Gen Intern Med*. 2019;34(34):1685–1778.
4. Stone Jr CA, Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. *Allergy*. 2020;75(2):273–288.
5. Fransson Sea. The importance of prolonged provocation in drug allergy – results from a Danish allergy clinic. *J Allergy Clin Immunol Pract*. 2017;5(5):1394–1401.
6. Robert R. Redfield M, Director. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. In: Prevention CfDCa, editor. 1 ed 2019.
7. *EU Comission. EU Guidelines for the Prudent Use of Antimicrobials in Human Health*. 2017.
8. Gouvernement TN. *National strategy against antibiotic resistance 2015-2020*. 2015.
9. Wurpts G, Aberer W, Dickel H, et al. Guideline on diagnostic procedures for suspected hypersensitivity to beta-lactam antibiotics. *Allergo Journal International*. 2019;28(5):121–151.
10. Collingridge DS, Gantt EE. The quality of qualitative research(.). *Am J Med Qual*. 2019;34(5):439–445.
11. Collingridge D. Validating a Questionnaire Available from: https://www.methodspace.com/blog/validating-a-questionnaire..
12. Tsang S, Royse CF, Terkawi AS. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi J Anaesth*. 2017;11(Suppl 1):S80–S89.
13. Delbecq AL. A group process Model for problem identification and program planning. *J Appl Behav Sci*. 1971;7(4):466–492.
14. Taylor E. We agree, don't we? The Delphi method for health environments research. *Health Environments Research & Design Journal*. 2020;13(1):11–23.
15. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69(4):420–437.
16. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. *Allergy*. 2020;75(6):1300–1315.
17. Dona I, Torres MJ, Montanez MI, Fernandez TD. *In vitro* diagnostic testing for antibiotic allergy. *Allergy Asthma Immunol Res*. 2017;9(4):288–298.
18. Chua KYL, Vogrin S, Bury S, et al. The penicillin allergy delabeling program: a multicenter whole-of-hospital health services intervention and comparative effectiveness study. *Clin Infect Dis*. 2021;73(3):487–496.
19. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321(2):188–199.
20. chiriac AM. Controversies in drug allergy: drug allergy pathways. *J Allergy Clin Immunol Pract*. 2019;7(1):46–60.
21. David A, Khan M, a. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol*. 2022;150(6):1333–1393.
22. Garvey LH, et al. *Danish guidelines on antibiotic allergy*; 2019. https://danskallergi.dk/wp-content/uploads/DSA-Retningslinjer-for-udredning-antibiotika-allergi-final-23.06.2019.pdf.
23. Jan S. Nurses as adverse drug reaction reporting advocates. *Eur J Cardiovasc Nurs*. 2022.
24. Van De Sijpe G, Gilissen L, Vandebotermet M, Peetermans WE, Spriet I, Schrijvers R. *Non-invasive Delabeling and Refining of Beta-Lactam Allergy Labels in Inpatients to Optimize Antimicrobial Stewardship*. 2022. Allergy.
25. Song YC, Nelson ZJ, Wankum MA, Gens KD. Effectiveness and feasibility of pharmacist-driven penicillin allergy de-labeling pilot program without skin testing or oral challenges. *Pharmacy*. 2021;9(3).
26. Jani YH. Sustaining and spreading penicillin delabeling: a narrative review of the challenges for service delivery and patient safety. *Br J Clin Pharmacol*. 2020;83:548–559.
27. Sara F. Inconsistencies in penicillin allergy labels in hospital and primary care after allergy investigation. *Clin Exp Allergy*. 2023;53(9):969–973.
28. Powell N, Wilcock M, Roberts N, Sandoe J, Tonkin-Crine S. Focus group study exploring the issues and the solutions to incorrect penicillin allergy-labelled patients: an antibiotic stewardship patient safety initiative. *Eur J Hosp Pharm*. 2021;28(2):71–75.
29. Devchand M. Pathways to improved antibiotic allergy and antimicrobal stewardship practice- the validation of a beta-lactam antibiotic allergy assesment tool. *Joural of Allergy and clinical immunology Pract*. 2019;7(3):1063–1065.
30. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med*. 2012;22(3):276–282.
31. Norwegian national guideline for the use of antibiotics in Hospitals 2023 Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus..
32. Stephanie Albin SA. Prevalence and Characteristics of Reported Penicillin Allergy in an Urban Outpatient Adult Population.
33. Norwegian immigration statistics. https://www.ssb.no/en/befolkning/innvandrere/statistikk/innvandrere-og-norskfodte-med-innvandrerforeldre..
34. Gilissen L. Prevalence of antibiotic allergy labels in a tertiary referral center in Belgium. *J Allergy Clin Immunol Pract*. 2021;11(6):2415–2425.
35. Borch. *The Prevalence of Suspected and Challenge-Verified Penicillin Allergy in University Hospital Population*. In: *Basic and Clinical Pharmacology and Toxicology*. vol. 98. 2006.
36. al . VSMPe. Urticaria: The 1-1-1 criterion for optimized risk stratification in β-lactam allergy delabeling. J Allergy Clin Immunol Pract. 2021;9(10):3697-3704.
37. Sara Fransson Hmm, Dmsc, Mogens Kappel Md, Dmsc, Janni Hjortlund Md, PhD, Lars K. Poulsen PhD, Dmsc, Ask D. Kvisselgaard, Lene H. Garvey Md, PhD. The importance of prolonged provocation in drug allergy – results from a Danish allergy clinic. J Allergy Clin Immunol Pract. 2017;5(5):1394-1401.
38. Bittner A. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc*. 2004;25(3):161–164.
39. Dona I. Resensitization in suspected penicillin allergy. *Allergy*. 2022;78(1):214–224.