AMJ Australasian Medical Journal [AMJ 2024;17(1):1138-1142]

# True Penicillin Drug Allergy

Loie Goronfolah[1,2,3*], Karen Ting Hie Hee[3], Ahmed Alsulami[1,2], Khalid Almufarriji[1,2], Fahad Okal[1,2], Abobaker Alshegaifi[1,2]

[1]Department of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[2]King Abdullah International Medical Research Center, Jeddah, Saudi Arabia.
[3]Ministry of the National Guard – Health Affairs, Jeddah, Saudi Arabia

## RESEARCH

Please cite this paper as: Goronfolah L, Hie Hee KT, Alsulami A, Almufarriji K, Okal F, Alshegaifi A. True Penicillin Drug Allergy. AMJ 2024;17(1):1138-1142.
https://doi.org/10.21767/AMJ.2023.4012

**Corresponding Author:**
Loie Goronfolah
Department of Allergy & Immunology,
King Saud bin Abdulaziz University for Health Sciences,
Jeddah, Saudi Arabia
goronfolahlo@ngha.med.sa

## ABSTRACT

**Introduction**

A drug allergy is an abnormal immune system reaction to a medication. Any medication can induce a drug allergy. However, a drug allergy is more likely with certain medicines, one of which is penicillin. The most common signs and symptoms of drug allergy are hives, rash, or fever. Up to 15.6 Per Cent of patients self-reported having an allergy to penicillin, and most of those reported allergies lacked proper documentation. In addition, 90 percent of penicillin-allergic patients can tolerate penicillin and, therefore, are labeled unnecessarily. Using alternative broad-spectrum antibiotics in those patients prevents optimal medical care. Skin tests provide confirmatory evidence of sensitization to a given allergen.

Therefore, the primary objective of this study is to estimate the prevalence of penicillin drug allergy by medical chart review and to identify the true drug-allergic patients.

**Methodology**

This is a retrospective observational study of the population by reviewing charts. The inclusion criteria were all patients labelled allergic to penicillin at KAMC between 1982 and December 2017. The second objective is a prospective interventional study of a skin prick and Intradermal Test (IDT) for penicillin allergy. We calculated the sample size, and the total required number of patients for the testing was 133.

**Results**

2738 labeled allergic patients, 455 were labeled as penicillin allergy (16.6 Per Cent). The majority were female participants, accounting for 338 (74.3 Per Cent). Table 1 shows the baseline characteristics. Among all the participants, maculopapular rash was the most common documented symptom. Moreover, 18.7 Per Cent (n=85) of the patients had either unknown or undocumented reactions. Penicillin drugs were classified into subgroups in which patients reacted. Penicillin (63.3 Per Cent) was the most common, followed by Augmentin (15.8 Per Cent), then amoxicillin (11.0 Per Cent). Thirty participants (6.6 Per Cent) received penicillin after they were labeled as allergic to penicillin and did not report any further reactions except for one participant who developed the rash.

**Conclusion**

As many as penicillin-labeled allergic patients, only a few are truly allergic to penicillin. This fact is attributed to poor documentation of allergies and based on the history taken from the patient that he might falsely relate a symptom or adverse effect to penicillin without being tested for penicillin allergy. This study recommends using proper documentation standards, such as penicillin skin tests when documenting patient allergies.

## Key Words

Penicillin, Adverse Drug Reaction, Hypersensitivity, IgE Mediated

## Introduction

Allergy is a well-known, serious adverse event that has concerned healthcare providers, especially when it is related to the treatment of different diseases. Antimicrobial drugs are the most common cause of type I hypersensitivity reactions, especially beta-lactams. Based on the hospital policy, which we will conduct our study, APP guidelines 1433-16 for allergy status documentation, "If there is a

known allergy to any substance, the following signed and dated entries will be documented by the physician in the progress notes and on all drug prescriptions."

Approximately 25 Per Cent of patients who required an antimicrobial drug reported an allergy to one of them, with up to 15.6 Per Cent of patients self-reported having a penicillin allergy, and most of those reported allergies lacked proper documentation, for example, the nature and the severity of the allergic reaction[1]. In addition, 90 percent of penicillin-allergic patients can tolerate penicillin and, therefore, are labeled unnecessarily[2-4]. Lutomski DM, et al. found that 198 Patients out of 416 labeled as allergic to different types of drugs reported a penicillin allergy, followed by sulfonamides, cephalosporins, macrolides, and fluoroquinolones. Penicillin and cephalosporin allergies were reported as strong causes of altered therapy, which might impact the patient's outcome[5].

The use of broad-spectrum antibiotics in patients labeled as allergic to penicillin is associated with higher costs and an increased risk of developing drug-resistant microbial agents. It may prevent optimal medical care. Inpatients who are allergic to penicillin and, hence, treated with broader spectrum drugs cost 63 Per Cent more compared to the controls. Moreover, in outpatients, the cost has increased by about 38 Per Cent[6].

Skin tests provide confirmatory evidence of sensitization to a given allergen. They are simple, quick to perform, cost-effective, highly sensitive, and essential for allergy diagnosis [7]. A study comparing various skin prick devices (single-headed versus multi-headed devices) shows that the sensitivity of skin prick tests ranges from 86 Per Cent to 97 Per Cent, and their specificity reaches 98 Per Cent or greater [8]. Intradermal tests are more reproducible and sensitive than skin prick tests, although false positive reactions are more common [9, 10].

## Methodology

### Study Area & Study Subjects

We studied in the Ambulatory Care Center (ACC), clinic 2, King Abdulaziz Medical City (KAMC), Jeddah, Saudi Arabia. The primary objective's inclusion criteria include all patients labelled as penicillin allergic. The exclusion criteria consist of all patients who are contraindicated to the skin test: People with a higher risk of anaphylaxis in response to the skin test, which includes poorly controlled asthma, reduction of lung function, and people with a history of severe reactions, recent anaphylaxis within the previous month, skin conditions including demography, acute or chronic urticaria, and cutaneous microcytosis because false positive are common. Patients unable to discontinue medications that interfere with the test results, like Antihistamine, H2 receptor antagonist, topical glucocorticoids, omalizumab, and tacrolimus, are also excluded. Patients on beta-two antagonists and angiotensin-converting enzyme antagonists are also excluded because they interfere with the treatment of anaphylactic reaction management.

### Study Design

The objective is a retrospective observational population study by reviewing charts. The inclusion criteria were all patients labelled allergic to drugs at KAMC between 1982 and December 2017. The exclusion criteria were non-antimicrobial agents.

### Sample Size & Sampling Technique

The total number of patients labeled allergic from 1982 to December 2017 is 2738. The number of penicillin-allergic patients is 540. We calculated the sample size using the Raosoft sample size calculator available at www.raosoft.com/samplesize.html. The confidence interval we estimated for the sample size is 95 Per Cent, with a margin of error of 5 Per Cent. The estimated response distribution is 10 Per Cent. The required minimal sample size is 111. The total required number of patients is 133, accounting for a 20 percent nonresponse rate. We randomly used computer numbers to select our sample size. Regarding the secondary objective, we included all patients labeled as allergic in the hospital since we estimated the prevalence.

Data collected from medical records and skin testing were collected in data collection sheets using Excel software. Based on the collected data, we estimated the prevalence of each drug allergy. Several patients with negative skin tests were also managed. Further investigations included categorizing the patients based on antimicrobial agents, demographics, and other study variables. Therefore, we calculated the percentage of truly penicillin-allergic patients, and data were analyzed using the SPSS program.

## Results

### Participants

2738 patients in our center, 455 were labelled penicillin allergy (16.6 Per Cent). Male participants were only 117 (25.7 Per Cent), and the majority were female, accounting for 338 (74.3 Per Cent). The mean Age of the participants was 47.82 years (± SD 21.83), ranging from 4 to 100 years. Table 1 shows the baseline characteristics.

As shown in Table 1, there is a significant variation between the time taken to segment these solid organs and bowel structures with the longest duration on segmenting small and large intestines.

**Presentation**

Participants who had allergic reactions presented with a wide variety of symptoms. Among all the participants, the maculopapular rash was the most common documented symptom, representing 63.1 Per Cent (n=287), followed by urticaria, accounting for 6.2 Per Cent (n=28). Anaphylaxis was present in 5.3 Per Cent (n=24), gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal cramps in 2.9 Per Cent (n=13), respiratory symptoms including

Shortness of breath, cough, sneezing, and wheezing in 2.6 Per Cent (n=12), angioedema in 1.8 Per Cent (n=8). Other patients had reactions that did not fall into these categories, including swelling, dizziness, palpitation, chest pain, tinnitus, and weakness, which accounted for 5.3 Per Cent (n=24). However, a small portion of the participants presented with more than one symptom. Moreover, 18.7 Per Cent (n=85) of the patients had either unknown or undocumented reactions.

**Drugs**

Penicillin drugs were classified into subgroups, in which patients who reacted to penicillin; Augmentin, amoxicillin, ampicillin, tazocin, piperacillin, flucloxacillin, oxacillin, and combined drugs were separately shown in Table 2.

Thirty participants (6.6 Per Cent) received penicillin after being labeled as allergic. They did not report any further reactions except one participant who developed a rash after re-exposure.

## Discussion

Our study found that about 16.6 Per Cent of the total patients labeled as allergic to drugs and food are allergic to penicillin, which was supported by another study that found around 15.6 Per Cent of the total labeled allergies were labeled as penicillin allergies. We compared penicillin to all other drug allergies, including food, antibiotics, and other medication allergies. Other studies have compared penicillin to only antibiotics[11] or all medication allergies[12]. Data were collected from two different methods in our center: electronic medical records via the Best Care system and paper-based medical records in which files are reviewed. The findings of many patients were different, as we noticed at the time of collecting data between the paper and electronic medical records, specifically, the dates and type of allergic reactions, and this issue was solved by writing the most reliable documented data in paper files. Unfortunately, none of the recorded histories mentioned the immediate or delayed reactions nor the severity of these reactions, which presents a problem mentioned in US studies [13,14].

We found that most patients with a penicillin allergy are female patients, which was also reported by other previous studies[15]. Because our study is retrospective, we are unsure if this was due to bias while saying or actual drug allergy. The mean Age of our patients was around 48 years, which was based on the Age at the time of the study, as there were no exact dates of the allergic events in almost all patients. A study also suggested that increasing Age and female sex are factors leading to a higher prevalence of antibiotic allergy[16], and most of our patients are adults or elderly (81.6 Per Cent).

Drug reactions varied between maculopapular rash being the most common (63.1 Per Cent) and angioedema being the least common (1.8 Per Cent). Similar studies have also reported these findings in the literature, as shown in Table 3. However, about 18 Per Cent of the participant's allergic reaction descriptions were either unknown or undocumented.

The limitations of our study were that the date of documentation for some patients needed to be included during the data retrieval because of the transition from paper-based to electronic medical records in our center in July 2016. Furthermore, 95 patients are required to be included. Another limitation was that almost none of the participants' files described the severity of the allergic reaction, nor did they differentiate between immediate and delayed reactions.

## Conclusion

As many as penicillin-labeled allergic patients there were, only a few are truly allergic to penicillin. This fact is attributed to poor documentation of allergies and based on the history taken from the patient that he might falsely relate a symptom or adverse effect to penicillin without being tested for penicillin allergy. This study recommends using proper documentation standards, such as penicillin skin tests when documenting patient allergies.

## References

1. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med. 2000;160(18):2819-22. Doi:10.1001/archinte.160.18.2819
2. Sogn DD, Evans R, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Ann Intern Med.1992;152: 1025–1032. Doi: 10.1001/archinte.1992.00400170105020
3. Gadde J, Spence M, Wheeler B, et al. Clinical experience with penicillin skin testing in a large inner-city STD clinic. JAMA. 1993;270: 2456-2463. Doi:10.1001/jama.1993.03510200062033
4. Solensky R, Khan D. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105:259e273. Doi: https://doi.org/10.1016/j.anai.2010.08.002
5. Lutomski DM, Lafollette JA, et al. Antibiotic allergies in the medical record affect drug selection and validity assessment. Pharmacotherapy. 2008;28(11):1348-53.
6. Sade K, Holtzer I, Levo Y, et al. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy. 2003;33:501-6. Doi: https://doi.org/10.1046/j.1365-2222.2003.01638.x
7. Chiriac AM, Bousquet J, Demoly P, et al. Middleton's allergy principles and practice.
8. Carr WW, Martin B, Howard RS, et al. Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology. Comparison of test devices for skin prick testing. J Allergy Clin Immunol. 2005;116:341-346.
9. Nelson HS, Oppenheimer J, Buchmeier A, et al. An assessment of the role of intradermal skin testing in diagnosing clinically relevant allergy to timothy grass. J. Allergy Clin Immunol. 1996; 97:1193. Doi: https://doi.org/10.1016/S0091-6749(96)70184-7
10. Wood RA, Phipatanakul W, Hamilton RG, et al. A comparison of skin prick tests, intradermal skin tests, and RASTs in diagnosing cat allergy. J Allergy Clin Immunol. 1999; 103:773.Doi: https://doi.org/10.1016/S0091-6749(99)70419-7
11. Jung IY, Kim JJ, Lee SJ, et al. Antibiotic-related adverse drug reactions at a Tertiary Care Hospital in South Korea. BioMed research international. 2017.
12. Chen JR, Tarver SA, Alvarez KS, et al. A proactive approach to penicillin allergy testing in hospitalized patients. J Allergy Clin Immunol Pract. 2017;5(3):686-93. Doi: https://doi.org/10.1016/j.jaip.2016.09.045
13. Shah NS, Ridgway JP, Pettit N, et al. Documenting penicillin allergy: The impact of inconsistency. PLOS ONE. 2016;11:e0150514. Doi: https://doi.org/10.1371/journal.pone.0150514
14. Moskow JM, Cook N, Champion-Lippmann C, et al. We are identifying opportunities in EHR to improve the quality of antibiotic allergy data. J Am Med Inform Assoc. 2016; 23: e108–12.Doi: https://doi.org/10.1093/jamia/ocv139
15. Macy E, Poon KYT. Self-reported Antibiotic Allergy Incidence and Prevalence: Age and Sex Effects. Am J Med. 2009;122(8):778.e1-778.e7. Doi: https://doi.org/10.1016/j.amjmed.2009.01.034
16. Macy E, Romano A, Khan D. Practical Management of Antibiotic Hypersensitivity in 2017. J Allergy Clin Immunol Pract. 2017;5(3):577-586. Doi; https://doi.org/10.1016/j.jaip.2017.02.014

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[3]Ministry of the National Guard – Health Affairs, Jeddah, Saudi Arabia

## Tables

**Table 1: Patients' characteristics.**

| | |
|---|---|
| **Gender (%)** | |
| Female | 338 (74.3) |
| Male | 117 (25.7) |
| Mean Age in years (SD) | 47.82 (± 21.83) |
| **Age in years** | |
| Minimum | 4 |
| Maximum | 100 |
| **Type of reaction (%)** | |
| Rash | 287 (63.1) |
| unknown | 85 (18.7) |
| Urticaria | 28 (6.2) |
| Anaphylaxis | 24 (5.3) |
| Gastrointestinal | 13 (2.9) |
| Respiratory | 12 (2.6) |
| Angioedema | 8 (1.8) |
| Other | 24 (5.3) |
| **Presentation (%)** | |
| single reaction | 346 (76.0) |
| Multiple reactions | 24 (5.3) |
| Unknown | 85 (18.7) |
| **Drug received after labelling (%)** | |
| Yes | 30 (6.6) |
| No | 425 (93.4) |

**Table 2: Frequency of allergy to each type of the penicillin family.**

| Class of allergic drug | Frequency | Percent |
|---|---|---|
| Penicillin | 288 | 63.3 |
| Augmentin | 72 | 15.8 |
| Amoxicillin | 50 | 11 |
| Tazocin | 8 | 1.8 |
| Ampicillin | 8 | 1.8 |
| penicillin & ampicillin | 3 | 0.7 |
| penicillin & amoxicillin | 6 | 1.3 |
| amoxicillin & augmentin | 6 | 1.3 |
| penicillin & tazocin | 3 | 0.7 |
| amoxicillin & ampicillin | 1 | 0.2 |
| penicillin & augmentin | 8 | 1.8 |
| oxacillin & ampicillin | 1 | 0.2 |
| flucloxacillin | 1 | 0.2 |
| Total | 455 | 100 |

**Table 3: Frequency of allergy to each type of the penicillin family.**

| Study (population number) | Joshua M, et al.[7] (n=3431) | Albin S, et al.[6] (n=1348) | Our study (n=455) |
|---|---|---|---|
| **Culprit drug** | **Penicillin** | **Penicillin** | **Penicillin** |
| **Reactions (%)** | | | |
| **Rash** | 53 | 37 | 63.1 |
| **Unknown** | - | 20.2 | 18.7 |
| **Urticaria** | 2.2 | 18.9 | 6.2 |
| **Anaphylaxis** | 12.5 | 6.8 | 5.3 |
| **Gastrointestinal** | - | 1.9 | 2.9 |
| **Respiratory** | - | 3.4 | 2.6 |
| **Angioedema** | 3.5 | 11.8 | 1.8 |
| **Other** | - | 5.3 | 5.3 |

***Received:*** *26-Dec-2023, Manuscript No. AMJ-24-4012;* ***Editor assigned:*** *29-Dec-2023, PreQC No. AMJ-24-4012(PQ);* ***Reviewed:*** *12-Jan-2024, QC No. AMJ-24-4012;* ***Revised:*** *17-Jan-2024, Manuscript No. AMJ-24-4012(R);* ***Published:*** *23-Jan-2024*