



The evaluation of penicillin allergy in dialysis patients

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Patients on hemodialysis and peritoneal dialysis are at high risk of developing infections and consume a large amount of antibiotics [1]. A label of penicillin allergy often leads to unnecessary avoidance of β -lactams and to the use of alternative classes of antibiotics [2]. However, according to recent studies penicillin allergy is grossly overdiagnosed [3]. In developed countries, approximately 10% of the population reports a penicillin allergy, with higher rates reported by older and hospitalized patients. When appropriately tested, more than 95% of those suspected of having a penicillin allergy actually tolerate penicillin [3].

The use of alternative antibiotic regimens may lead to treatment failure and increases the risk of antimicrobial resistance and *Clostridioides difficile* infection [4]. In a study comparing cephalosporins and vancomycin in the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia among hemodialysis patients, the risk of treatment failure was three times more likely when vancomycin was used [5].

Traditionally, removing the penicillin allergy label has required a thorough allergological evaluation, including skin testing, thus making it difficult to implement for larger patient groups. A recent review by The American Academy of Allergy, Asthma, and Immunology (AAAAI), the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) suggests a direct amoxicillin challenge to be safe and effective in patients defined as low risk for penicillin allergy [3].

The present study was conducted in Pirkanmaa Health District, Finland, with a catchment population of 540 000 inhabitants. In this area, dialysis treatment is given only in Tampere University Hospital and its six satellite units, with a total of 211 patients, 181 on hemodialysis and 30 on peritoneal dialysis.

As a part of an antibiotic stewardship initiative, we conducted a project to assess the prevalence of penicillin allergy among patients receiving dialysis and the possibility of removing the penicillin allergy labels documented in their electronic health record (EHR). Results of the project were analyzed retrospectively. Permission to conduct this study was

granted by the research director of the Research Services of the Pirkanmaa Hospital District.

All patients receiving dialysis treatment were included in the study. Of the study population, infectious diseases specialist (S.S.) identified all patients labelled as penicillin allergic. Patients' EHRs, including details of previous medications, were examined. All patients with a history of penicillin allergy were interviewed by S.S. Figure 1 is a flow chart of the assessment of penicillin allergy correctness.

Patients with non-allergic symptoms related to penicillin use or to a history of receiving penicillin intentionally or unintentionally without any complications after the penicillin allergy label on their EHR, were directly de-labeled. The patients were informed about the decision.

If the reaction was pruritus without rash or had occurred over 10 years ago without features of immunoglobulin E (IgE)-mediated reactions, patients were defined as having a low risk and were eligible for amoxicillin challenge [3]. After informed consent, patients were given a direct amoxicillin challenge. Hemodialysis patients were given 250 mg oral amoxicillin during a dialysis treatment session and they were monitored for an hour. Peritoneal dialysis patients followed the same protocol during an outpatient visit.

Patients with a history of immediate IgE-mediated reaction were referred to an allergology specialist. If the allergic reaction had occurred within a year or it was interpreted as a serious delayed reaction, the penicillin allergy label was not removed.

We identified a total of 23 patients (21 HD and 2 PD) with a penicillin allergy label on their EHR. Thus, the prevalence of reported penicillin allergy was 11% (23/211).

Results of the penicillin allergy evaluation are given in Table 1. The penicillin allergy label was removed from 17 out of 23 (74%) patients. In nine patients the label was removed on the grounds of patients' history, and in eight after amoxicillin challenge. All patients given the amoxicillin challenge tolerated it and did not develop any symptoms. Three patients referred to allergology unit were all penicillin skin test negative, but despite this, a confirmatory oral amoxicillin challenge was not performed, and the penicillin allergy label could not be removed.

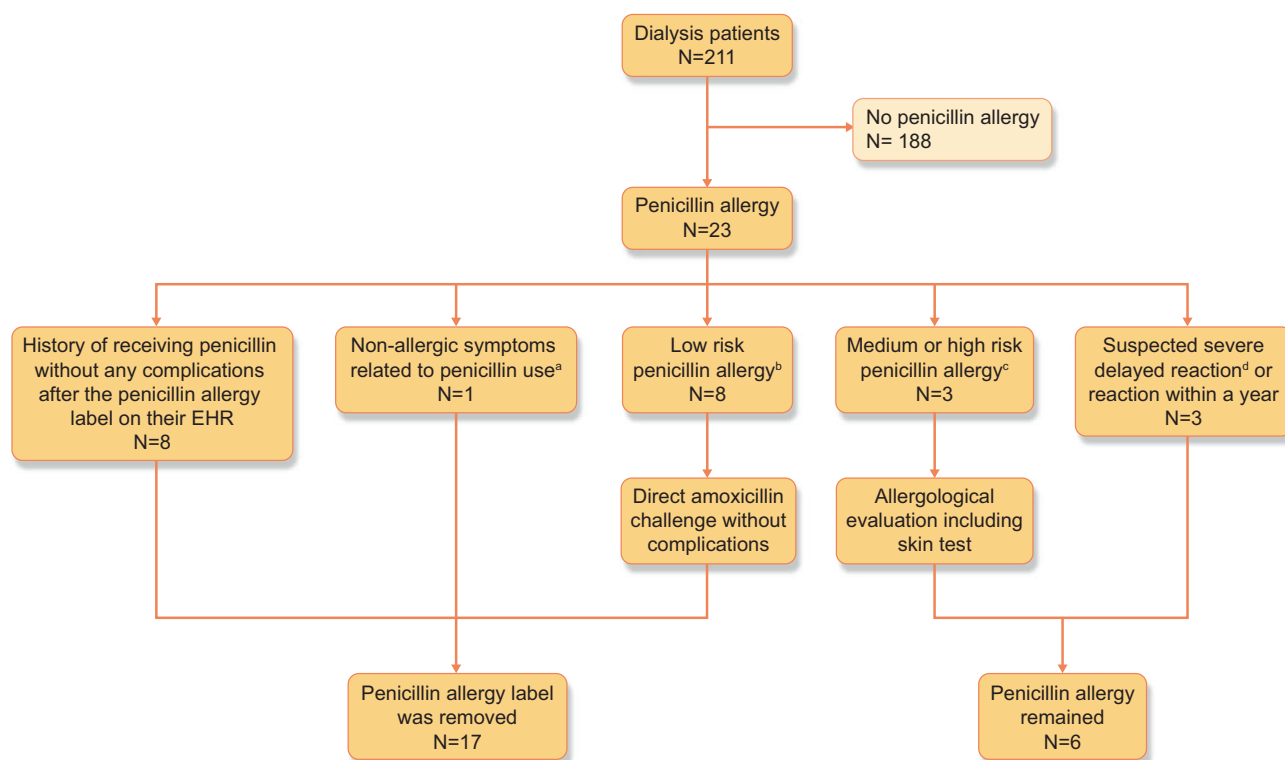


Figure 1: Description of the study patients. (a) Gastrointestinal symptoms, headaches, family history of penicillin allergy. (b) Pruritus without rash, reaction occurred 10 years ago without features of IgE-mediated reactions. (c) Urticaria, angioedema or anaphylaxis. (d) Severe cutaneous adverse reactions (SCAR), hemolytic anemia, an organ-specific reaction, drug fever or serum sickness.

Table 1: Results of the penicillin allergy evaluation.

Patient	Age (years)	Gender	Reaction type	Description	Time since reaction (years)	Re-exposure to penicillin after the allergy diagnosis	Result
1	75	M	Delayed	Diarrhea	>10	No	Penicillin allergy label was removed on the grounds of patients' history ^a
2	60	F	Delayed	Rash	>10	Yes	
3	63	F	Delayed	Rash	>10	Yes	
4	74	M	Delayed	Blistering of the finger tips	>10	Yes	
5	61	M	n/a	Tingling sensation in mouth	1–10	Yes	
6	72	M	n/a	No memory	>10	Yes	
7	50	F	n/a	Rash	>10	Yes	
8	51	F	n/a	Uncomfortable sensation in throat	>10	Yes	
9	78	M	Delayed	Rash	>10	Yes	Penicillin allergy label was removed after direct amoxicillin challenge
10	70	M	Delayed	Cracked lips	>10	No	
11	84	M	Delayed	Metallic taste in mouth	>10	No	
12	63	F	Delayed	Pruritus without rash	1–10	No	
13	71	M	Delayed	Peeling fingertips	>10	No	
14	75	M	n/a	No memory	>10	No	
15	63	F	Delayed	Rash	>10	No	
16	37	F	Delayed	Rash	>10	No	
17	75	F	Delayed	Rash	>10	No	Referred to allergologist, penicillin allergy retained
18	38	F	Immediate	Fever, hives	>10	No	
19	73	M	Immediate	Shortness of breath, syncope	>10	No	
20	68	F	Immediate	Widespread rash	>10	No	Not further evaluated, penicillin allergy retained
21	82	F	Delayed	Fever, abscesses (suspected AGEP)	>10	No	
22	77	F	Immediate	Hives, swelling of lips	<1	No	
23	67	M	Delayed	Pruritic rash	<1	No	

^aReaction was non-allergic or patient had an exposure to penicillin after the allergy diagnosis.

M, male; F, female; n/a, not available; AGEP, acute generalized exanthematous pustulosis.

In conclusion, we were able to safely de-label three-quarters of our dialysis patients with a history of penicillin allergy without a consultation by an allergologist. This was possible with an adequate evaluation of patient history in nine patients and by a simple oral amoxicillin challenge in eight patients. The protocol was adopted from a review published in 2019 [3]. A more recent guideline published by AAAAI and the American College of Allergy, Asthma and Immunology (ACAAI) suggests that the amoxicillin challenge could be performed in an even greater proportion of patients [6].

In Finland dialysis treatment is provided mainly by public hospitals throughout the whole country, and we have a good collaboration between infectious diseases specialists and nephrologists. There might be limitations to the generalizability of precisely this protocol to other dialysis centers in Europe and elsewhere in the world. However, there is a global need to improve antimicrobial stewardship among dialysis patients [7]. We provide evidence that simple and inexpensive methods can be used to de-label most penicillin allergies in dialysis patients, potentially improving future antibiotic therapy and reducing adverse outcomes. We recommend implementing a systematic penicillin allergy evaluation as a part of the routine care of dialysis patients.

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AUTHORS' CONTRIBUTIONS

Research idea and study design was by S.S., M.H., R.H., S.M. and J.S.; data acquisition was performed by S.S.; data

analysis/interpretation was carried out by S.S. and M.H.; supervision or mentorship was provided by M.H., R.H., S.M. and J.S. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no relevant financial interests to disclose.

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