



## Association between chronic urticaria and self-reported penicillin allergy

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### ABSTRACT

**Background:** Penicillin allergy is the most commonly reported drug allergy and often presents with cutaneous symptoms. Other common diagnoses, such as chronic urticaria, may be falsely attributed to penicillin allergy. Because chronic urticaria is fairly common in the general population, evaluation of its prevalence in patients with self-reported penicillin allergy was of interest. Similarly, the prevalence of self-reported penicillin allergy in patients with chronic urticaria is not well known and also becomes interesting in light of the high prevalence of self-reported penicillin allergy in the general population.

**Objectives:** To determine the prevalence of self-reported penicillin allergy in patients with chronic urticaria and the prevalence of chronic urticaria in patients with self-reported penicillin allergy.

**Methods:** This was a retrospective medical record review of 11,143 patients completed using the electronic health record of the University of Pennsylvania Allergy and Immunology clinic.

**Results:** The prevalence of self-reported penicillin allergy in patients with chronic urticaria was found to be approximately 3 times greater than in the general population. The prevalence of chronic urticaria in patients with self-reported penicillin allergy was also found to be approximately 3 times greater than in the population.

**Conclusion:** This link between chronic urticaria and self-reported penicillin allergy highlights the need for clinicians to inquire about self-reported penicillin allergy in patients with chronic urticaria and to consider penicillin skin testing. Furthermore, patients who report penicillin allergy might actually have chronic urticaria, indicating the importance of inquiring about chronic urticaria symptoms in patients with self-reported penicillin allergy.

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### Introduction

Penicillin allergy is the most commonly reported antibiotic allergy.<sup>1</sup> Adverse reactions to penicillin have been reported since its introduction more than 70 years ago.<sup>1</sup> Approximately 10% of all patients report a history of penicillin allergy.<sup>2</sup> These adverse reactions often present with cutaneous eruptions, including urticaria and morbilliform rashes.<sup>1,3,4</sup> However, these signs and symptoms can have other causes. Thus, there exists the possibility that other common diagnoses, such as chronic urticaria or viral exanthems, can be mistaken for a drug allergy.<sup>2</sup>

Self-reporting of drug allergies is inherently subjective; thus, it is prudent to consider factors that may confuse, complicate, or

otherwise affect a patient's reported history. The diagnosis of chronic urticaria in particular may be a complicating component of a patient's self-reported penicillin allergy. Chronic urticaria is defined as urticaria with or without angioedema that is continuously or intermittently present for 6 weeks or longer.<sup>5,6</sup> Patients may attribute chronic urticaria to a specific cause, such as a medication or food, when its cause is in fact usually idiopathic in nature.<sup>6</sup> In addition, patients with chronic urticaria may inaccurately report a history of penicillin allergy by falsely attributing their urticaria to an adverse drug reaction.

Because chronic urticaria is fairly common, with an estimated prevalence of 0.5% to 5% and an estimated annual incidence of 1.4% depending on the population under study,<sup>6</sup> evaluation of its prevalence in patients with self-reported penicillin allergy was of interest. Similarly, the prevalence of self-reported penicillin allergy in patients with chronic urticaria is not well known and also becomes interesting in light of the high prevalence of self-reported penicillin allergy in the general population.

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Most patients who report a penicillin allergy are not found to be allergic on penicillin skin testing.<sup>1</sup> In large studies performed during the last decade, less than 5% of patients who have had penicillin skin testing had positive results.<sup>7</sup> Given the discrepancy between self-reported and skin test–proven penicillin allergy, an understanding of those patients who may overreport penicillin allergy is potentially valuable because these patients can be targeted for skin testing.

Furthermore, in view of the increased health care–associated costs of penicillin allergy, including longer hospital stays and unnecessary use of broad-spectrum antibiotics with associated serious infections and drug resistance,<sup>8</sup> the focused evaluation of patients with higher than expected rates of self-reported penicillin allergy is essential. This study attempts to shed light on and better understand the characteristics of one such group of patients.

We hypothesized that the prevalence of chronic urticaria in patients with self-reported penicillin allergy would be higher than in the general population. We also hypothesized that the prevalence of self-reported penicillin allergy in patients with chronic urticaria would be higher than in the general population.

## Methods

The study was a retrospective medical record review completed using the electronic health record of the University of Pennsylvania Health System. Medical records of all patients 18 years or older seen in the University of Pennsylvania Allergy and Immunology Clinic from June 12, 2007, until August 8, 2014 (the date that the electronic medical record was instituted until the start of the study), were screened to identify 2 sets of patients: those with self-reported penicillin allergy and those with chronic urticaria. Self-reported penicillin allergy was defined by the presence of penicillin, amoxicillin, amoxicillin-clavulanate, or piperacillin-tazobactam on the allergy list of the electronic health record. Chronic urticaria was defined as a diagnosis in the medical record of urticaria present for 6 weeks or longer. Patients with cold-induced urticaria, solar urticaria, cholinergic urticaria, and physical urticaria (including dermatographism) were included in the study if their urticaria had been present for longer than 6 weeks.

Medical record review was performed by one of the authors (S.S.) in the Section of Allergy and Immunology at the University of Pennsylvania Health System. A sample group of 20 medical records was reviewed to ensure accuracy of data collection by one of the authors (A.A.). There were no discrepancies in data collection within this sample group of medical records.

The records of patients with self-reported penicillin allergy were reviewed to identify the presence of any diagnosis of urticaria; those records were then examined to determine whether urticaria was chronic. The prevalence of chronic urticaria within the cohort of patients with self-reported penicillin allergy was then compared with the prevalence of chronic urticaria in all clinic patients without self-reported penicillin allergy as well as the estimated prevalence of chronic urticaria in the general population.

The records of patients with chronic urticaria were reviewed to identify the presence of self-reported penicillin allergy, as defined above. The prevalence of self-reported penicillin allergy within the cohort of patients with chronic urticaria was then compared with the prevalence of self-reported penicillin allergy in all clinic patients without chronic urticaria as well as the estimated prevalence of self-reported penicillin allergy in the general population.

The records of all patients with both chronic urticaria and self-reported penicillin allergy were then abstracted for demographic information (age, sex, and race), presence of several comorbidities (diagnoses associated with frequent use of antibiotics, eg, sinusitis, pneumonia, or immunodeficiency, and diagnoses that may be associated with urticaria, eg, autoimmune disease or malignancy),

use of certain types of medications associated with urticaria or angioedema (nonsteroidal anti-inflammatory drugs [NSAIDs], opiates, hormones, angiotensin-converting enzyme [ACE] inhibitors), and penicillin skin test results, if testing had been performed. In addition, medical record review looked for the date of onset of chronic urticaria, date and type of index reaction to penicillin, alcohol use (which may be associated with urticaria<sup>5</sup>), and type of other drug allergies (categorized by any other drug, any other antibiotic, any other  $\beta$ -lactam antibiotic, contrast dye, NSAIDs, and ACE inhibitors).

The institutional review board of the Perelman School of Medicine, University of Pennsylvania, approved the study and waived the requirement for individual patient consent.

## Results

The medical records of 11,143 unique patients seen in the clinic during the specified date range were reviewed to identify a total of 220 patients with both self-reported penicillin allergy and chronic urticaria. The demographic characteristics of the 220 patients with both self-reported penicillin allergy and chronic urticaria are given in Table 1. Most of the patients were female, with a median age of 49 years. Approximately half of the patients self-identified as white, and a third self-identified as black. Almost three-quarters (71%) reported drug allergy to at least one other medication. Given the possible association between alcohol use and urticaria in some patients with chronic urticaria,<sup>5</sup> we found that approximately 47% reported alcohol consumption (in varying frequencies, from daily to rare use).

Of 11,143 patients, 1,332 (12.0%) had any diagnosis of urticaria and 666 patients (6.0%) had chronic urticaria on medical record review, of which 220 (33.0%) had self-reported penicillin allergy (Table 2). Of the 1,516 patients with self-reported penicillin allergy,

**Table 1**

Demographics and characteristics of 220 patients with self-reported penicillin allergy and chronic urticaria<sup>a</sup>

| Characteristic                       | No. (%) of patients |
|--------------------------------------|---------------------|
| Female                               | 187 (85.0)          |
| Race                                 |                     |
| White                                | 112 (50.9)          |
| Black                                | 74 (33.6)           |
| Hispanic                             | 8 (3.6)             |
| Asian                                | 5 (2.3)             |
| Other or unknown                     | 21 (9.6)            |
| Presence of comorbidities            |                     |
| Sinusitis                            | 27 (12.3)           |
| Pneumonia                            | 2 (0.9)             |
| Immunodeficiency, including HIV      | 4 (1.8)             |
| Autoimmune disease                   | 40 (18.2)           |
| Malignancy                           | 24 (10.9)           |
| Presence of other drug allergies     |                     |
| Any drug other than penicillin       | 156 (70.9)          |
| Any antibiotic                       | 89 (40.5)           |
| Any other $\beta$ -lactam antibiotic | 23 (10.5)           |
| Contrast dye                         | 20 (9.1)            |
| NSAIDs                               | 44 (20.0)           |
| ACE inhibitors                       | 16 (7.3)            |
| Use of certain medications           |                     |
| NSAIDs, including aspirin            | 65 (29.6)           |
| Opiates                              | 28 (12.7)           |
| Hormones                             | 38 (17.3)           |
| ACE inhibitors                       | 9 (4.1)             |
| Alcohol use                          |                     |
| Used alcohol                         | 104 (47.3)          |
| Did not use alcohol                  | 96 (43.6)           |
| Unknown                              | 20 (9.1)            |

Abbreviations: ACE, angiotensin-converting enzyme; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

<sup>a</sup>Patient age was as follows: mean, 51 years; range, 20 to 92 years; median, 49 years.

**Table 2**Prevalence of chronic urticaria and self-reported penicillin allergy in 11,143 patients<sup>a</sup>

|                                           | Positive diagnosis of chronic urticaria                     | No diagnosis of chronic urticaria                                  | Total                                                               |
|-------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------|
| Positive self-reported penicillin allergy | 220                                                         | 1,296                                                              | 1,516 (13.6)<br>(Patients with self-reported penicillin allergy)    |
| No self-reported penicillin allergy       | 446                                                         | 9,181                                                              | 9,627 (86.4)<br>(Patients without self-reported penicillin allergy) |
| Total                                     | 666 (6.0)<br>(Patients with diagnosis of chronic urticaria) | 10,477 (94.0)<br>(Patients without diagnosis of chronic urticaria) | 11,143<br>(Total unique patients seen in allergy clinic)            |

<sup>a</sup>Data are presented as number (percentage).

440 (29.0%) had a diagnosis of urticaria, and 220 (14.5%) had chronic urticaria on medical record review (Table 2). A total of 1,516 (13.6%) of 11,143 patients were found to have self-reported penicillin allergy; thus, 9,627 patients did not have self-reported penicillin allergy (Table 2). Of these 9,627 patients without self-reported penicillin allergy, only 446 (4.6%) had chronic urticaria, an estimate that is in line with the estimated 0.5% to 5% prevalence of chronic urticaria reported in the general population.<sup>6</sup> In contrast, the study's finding of 14.5% of patients with self-reported penicillin allergy with chronic urticaria is approximately 3 times higher.

A total of 1,296 patients with self-reported penicillin allergy did not have a diagnosis of chronic urticaria (Table 2). Thus, of all 10,477 patients seen in clinic without a diagnosis of chronic urticaria, only 12.4% had self-reported penicillin allergy. This estimate is similar to the estimated 10% prevalence of self-reported penicillin allergy in the general population. By comparison, the study's finding of 33.0% of patients with chronic urticaria with self-reported penicillin allergy is approximately 3 times higher.

Among the 220 patients with self-reported penicillin allergy and chronic urticaria, 112 (50.9%) had urticaria without angioedema and 59 (26.8%) had dermatographism, as noted on physical examination, described in a visit note, and/or listed as a diagnostic code in the medical record.

Comorbidities associated with possible increased antibiotic use, including sinusitis, pneumonia, and immunodeficiency, and conditions that may be associated with urticaria or angioedema, including autoimmune disease, are given in Table 1. Among the 220 patients, few had documented immunodeficiency or pneumonia, and approximately 12% had a history of sinusitis. Although the association between malignancies and urticaria is controversial, the medical records were also reviewed for the presence of malignancy. Nearly 11% had some type of malignancy (including skin cancer). More patients (18.2%) had an autoimmune disease, including thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus.

NSAIDs, opiates, hormones (including oral contraceptives), and ACE inhibitors can be associated with urticaria or angioedema (Table 1). Of note, NSAIDs, including aspirin, were found on nearly 30% of patients' medication lists.

More than 70% had documentation of at least one additional drug allergy. Of those, more than 40% had documentation of allergy to any other antibiotic and more than 10% to another  $\beta$ -lactam antibiotic.

The characteristics of the reported index reaction to penicillin are given in Table 3. Many patients reported cutaneous symptoms, typically hives, rash, and/or pruritus. Small numbers of patients reported having anaphylaxis or respiratory symptoms. Nearly a quarter of patients had symptoms unknown or not noted in the medical record. In addition, approximate date of index reaction to penicillin was only noted in 82 medical records (37.2%). If noted, an index reaction occurred during infancy (8 patients), childhood (31 patients), adolescence (9 patients), or adulthood (34 patients).

Unfortunately, penicillin skin testing had been performed in only 5 patients; 4 of 5 of these skin test results were negative. Those patients with a negative skin test result underwent a subsequent oral amoxicillin challenge, all of which produced negative results.

## Discussion

It is important to study self-reported penicillin allergy because even though less than 10% of those with self-reported penicillin allergy are truly allergic,<sup>8</sup> those who self-report penicillin allergy are treated differently. They are more often given broad-spectrum antibiotics, leading to a higher risk of acquiring antibiotic resistance or *Clostridium difficile* infection.<sup>8–10</sup> They may also have higher health care costs and longer hospitalizations.<sup>8–10</sup> This study finds an association between chronic urticaria and self-reported penicillin allergy, suggesting that in some patients, self-reported penicillin allergy may be due to chronic urticaria, not true drug allergy. Thus, for the optimal treatment of patients with self-reported penicillin allergy and chronic urticaria, the treating clinician should confirm the presence of IgE-mediated penicillin sensitization with penicillin skin testing, if dermatographism is not present and if clinically appropriate. Positive and negative control tests in addition to testing with penicillin determinants allow interpretation of testing even in patients with chronic urticaria.

Penicillin skin testing can be performed electively, when patients are “not in immediate need of antibiotic therapy,” or more urgently, “when treatment with a penicillin compound is contemplated.”<sup>2</sup> Patients with negative skin test results may then receive penicillin with “minimal risk of an IgE-mediated reaction,” and depending on the patient's reaction history, “the first dose of penicillin may need to be given via graded challenge.”<sup>2</sup> This type of targeted penicillin skin testing will clarify these patients' current penicillin allergy status, which may help to lower various health care costs associated with self-reported penicillin allergy.

**Table 3**

Characteristics of self-reported index reaction to penicillin in 220 patients with self-reported penicillin allergy and chronic urticaria

| Symptoms of index reaction           | No. (%) of patients<br>(N = 220) |
|--------------------------------------|----------------------------------|
| Hives                                | 84 (38.2)                        |
| Rash                                 | 45 (20.5)                        |
| Itching, pruritus                    | 13 (5.9)                         |
| Swelling, edema, throat closing      | 41 (18.6)                        |
| Shortness of breath, dyspnea, asthma | 13 (5.9)                         |
| Nausea, vomiting                     | 6 (2.7)                          |
| Diarrhea, abdominal pain             | 8 (3.6)                          |
| Anaphylaxis                          | 14 (6.4)                         |
| Serum sickness                       | 1 (0.5)                          |
| Syncope                              | 2 (0.9)                          |
| Convulsions                          | 1 (0.5)                          |
| Palpitations                         | 1 (0.5)                          |
| Other or unknown                     | 50 (22.7)                        |

In our study, 33.0% of patients with chronic urticaria had self-reported penicillin allergy, and 14.5% of patients with self-reported penicillin allergy had chronic urticaria. These prevalence rates are much higher than in the general population. Within the study population itself, there was a similar difference in prevalence noted as well. In contrast to self-reported penicillin allergy in 33.0% of patients with chronic urticaria, only 12.4% of all patients without chronic urticaria had self-reported penicillin allergy, and compared with a 14.5% rate of chronic urticaria in patients with self-reported penicillin allergy, the rate of chronic urticaria was only 4.6% in all patients without self-reported penicillin allergy. These lower prevalence rates are similar to those estimated for the general population.

Several explanations are possible for the unexpectedly high prevalence of self-reported penicillin allergy in our cohort with chronic urticaria and similarly high prevalence of chronic urticaria in patients reporting penicillin allergy. Although the exact timing of self-reported penicillin reaction and onset of chronic urticaria was not possible to ascertain on retrospective record review, many of the study patients had their self-reported index reaction to penicillin before development of chronic urticaria. Given the presence of chronic urticaria, these patients are likely to be more prone to rashes and urticaria throughout their lives, possibly due to increased skin sensitivity with a predisposition for cutaneous manifestations.

Once these patients developed chronic urticaria during adulthood, they may have been more likely to remember prior rash or hives as being an allergy to penicillin, thus leading to possible false recall of penicillin allergy. In addition, if a patient's self-reported index reaction to penicillin and onset of chronic urticaria did in fact occur close in time to each other, their self-reported penicillin allergy may simply have been chronic urticaria, falsely attributed to an adverse drug reaction.

This study has several limitations. This retrospective medical record review of data inputted into the electronic health record relied on manual entries, which are user dependent, error prone, and inherently subjective, given that much of the data are based on patients' self-reported histories. The study examined patients seen in an allergy and immunology clinic at one large academic medical center, presenting several selection biases. Patients seen at an allergy clinic may tend to have and/or report more allergies, including those to drugs. In addition, patients seen at a large academic medical center may be self-selecting or referred from other allergists in the community, possibly due to complicated medical (and specifically allergic) diagnoses. Nevertheless, the prevalence of chronic urticaria in those without self-reported penicillin allergy and the prevalence of self-reported penicillin allergy in those without chronic urticaria approximated that of the general population, suggesting that our study population without chronic urticaria or self-reported penicillin allergy was not that different from the general population.

Of interest, the rate of autoimmune disease found in this study population was also somewhat similar to that found in a 2012 study of patients with chronic urticaria, of whom 9.8% were found to have hypothyroidism,<sup>11</sup> thus speaking to the generalizability of the study's findings. By contrast, however, the nearly 27% prevalence rate of dermatographism found in the study population was fairly high, possibly due to increased questioning about and testing for dermatographism in patients with chronic urticaria.

Furthermore, although our retrospective medical record review found an association between self-reported penicillin allergy and chronic urticaria, it cannot shed any light on causality in either direction. In the same vein, it was not possible to determine the exact temporal association of the use of NSAIDs and other medications with onset of chronic urticaria or whether these medications exacerbated or triggered the patients' urticaria.

In addition, penicillin skin testing was only performed on a small number of patients with self-reported penicillin allergy, so the current presence of IgE-mediated sensitization to penicillin could not be ascertained. Penicillin skin testing was not performed on most of the study population likely because the patients were being seen in the clinic to address their urticaria and not their penicillin allergy. Finally, because of limited resources, it was not possible to explore the prevalence of antibiotic allergy in the rest of the allergy clinic population.

This study's surprising finding that chronic urticaria and self-reported penicillin allergy frequently coexist (specifically, 14.5% of patients who report penicillin allergy have chronic urticaria) highlights the need for clinicians to consider the possibility that a reported allergy to penicillin may in fact be due to chronic urticaria and not an adverse drug reaction. The finding that self-reported penicillin allergy exists in 33% of those with chronic urticaria further supports this possibility. Keeping this in mind, clinicians should remember to ask patients with self-reported penicillin allergy about symptoms of chronic urticaria. It is also possible that patients with chronic urticaria are more likely to have positive penicillin skin test results; however, without performing skin tests on all such patients, this cannot be determined.

Furthermore, in those patients with self-reported penicillin allergy and chronic urticaria, as long as dermatographism is not currently present, penicillin skin testing can be performed to evaluate for IgE-mediated sensitization to penicillin. By clarifying patients' current penicillin allergy status, this type of targeted penicillin skin testing may ultimately help to contain health care costs associated with self-reported penicillin allergy and, importantly, reduce patients' exposure to the risks of treatment resulting from the use of penicillin alternatives.

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