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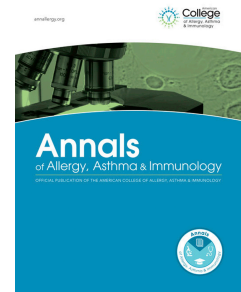
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Doctor, I am allergic to penicillin: Is this dangerous?

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1 A 52-year-old female is self-referred for evaluation of penicillin allergy. Her visit is prompted by
2 reading a story in *The New York Times*¹ about the dangers of being mislabeled as penicillin-allergic. Her
3 past medical history is notable only for hypertension which is controlled on lisinopril. She reports
4 receiving penicillin VK in college for Streptococcal pharyngitis and sometimes during the course
5 developing generalized urticaria, without any oropharyngeal, respiratory, cardiovascular or
6 gastrointestinal symptoms. The reaction was treated with oral antihistamines, resulting in rapid
7 resolution of the cutaneous eruption. She has not received any beta-lactam antibiotics since the
8 reaction. Two years prior to presentation, she was prescribed oral clindamycin by a dentist and
9 developed *Clostridium difficile* colitis, which required treatment with both oral metronidazole and oral
10 vancomycin to resolve. One year prior to presentation, the patient received oral ciprofloxacin for an
11 *Escherichia coli* urinary tract infection and developed Achilles tendonitis, from which she has not fully
12 recovered. Skin testing with Pre-Pen and penicillin G was negative, following which she tolerated an oral
13 challenge with 250 mg amoxicillin. The patient's penicillin allergy label was removed from her electronic
14 chart and pharmacy records.

15 Typically, an allergy, such as to foods or flying insects, raises concerns in patients due to a fear of
16 being exposed to the allergenic substance and experiencing a potentially severe or fatal reaction. On the
17 other hand, patients labelled penicillin-allergic do not generally fear reacting to the antibiotic, since
18 unintentional exposure is highly unlikely. However, what these individuals may not be aware of – and
19 what they should fear – is the morbidity, mortality and economic costs associated with the unnecessary
20 withholding of appropriate antibiotic therapy in patients mistakenly labeled as penicillin-allergic.
21 Allergists have long suspected this important and underappreciated aspect of penicillin allergy, but it
22 was not until the last decade that published studies have formally demonstrated detrimental clinical
23 consequences of “penicillin allergy.”

Penicillin allergy is self-reported by about 10% of the population, yet over 90% of these individuals are not truly allergic and are able to tolerate penicillins.² There are 2 main reasons for the discrepancy between self-reported and confirmed penicillin allergy. Some patients were mislabeled as allergic at time of their historical reaction, meaning they were never allergic at all, and their symptoms were misattributed to the antibiotic (such as viral-related urticaria or side-effects like headache or gastrointestinal symptoms.) Additionally, because penicillin-specific IgE antibodies wane over time, the natural history of penicillin allergy is resolution in most (but not all) patients.

Antibiotic options for patients reporting a penicillin allergy are limited, since many physicians avoid prescribing not just penicillins, but also cephalosporins and carbapenems to these individuals. Consequently, patients labelled penicillin-allergic, compared to those not labelled as such, are more likely to receive quinolones, vancomycin, clindamycin and macrolides. Treatment with these 2nd line antibiotics when a beta-lactam is preferred may not be as efficacious. For example, treatment of *Staphylococcus aureus* bacteremia with vancomycin results in more treatment failures compared to first line treatment with cefazolin. Additionally, many alternate non-beta-lactam antibiotics are less safe and associated with serious non-allergic adverse events, such as macrolide-linked fatal cardiac arrhythmia and quinolone-associated tendinopathy. Certain antibiotic-resistant bacteria, such as vancomycin resistant Enterococcus (VRE) are linked to previous use of quinolones and vancomycin. Quinolones and clindamycin are among the most common antibiotics leading to development of *Clostridium difficile* colitis. In the clinical vignette presented above, if the patient did not report a history of penicillin allergy, she likely would have received a penicillin instead of clindamycin for her dental infection. Similarly, her *E coli* urinary tract infection was sensitive to aminopenicillins, cephalosporins and quinolones (resistant to trimethoprim-sulfamethoxazole and nitrofurantoin), therefore she probably would have been treated with a beta-lactam antibiotic.

Macy et al was the first to demonstrate an association between being labeled penicillin allergic and negative clinical outcomes.³ Using a large centralized electronic medical record (EMR) database, patients with documented penicillin allergy were compared with matched control subjects (who were not labeled penicillin-allergic). Cases were significantly more likely than controls to receive fluoroquinolones (25% vs 14.3%, $p < 0.00001$), vancomycin (21.2% vs 12.4%, $p < 0.0001$), and clindamycin (24.4% vs 5.7%, $p < 0.0001$). Additionally, cases had 30.1% (95% CI, 12.5% to 50%) more VRE, 23.4% (95% CI, 15.6% to 31.7%) more *C difficile*, and 14.1% (95% CI, 7.1% to 31.7%) more methicillin-resistant *Staphylococcus aureus* (MRSA) than controls. The average hospital stay for cases was 0.59 days (9.9%; 95% CI, 0.47-0.71 days) longer than for control subjects. Blumenthal et al subsequently confirmed these findings in another large database, using a similar matched cohort of patients with and without documented penicillin allergy.⁴ They reported that cases were more likely to be treated with fluoroquinolones (11.8% vs 5.0%, $p < 0.001$), clindamycin (0.64% vs 0.15%, $p < 0.001$), macrolides (59.6% vs 13.5%, $p < 0.001$), and tetracyclines (22.8% vs 12.0%, $p < 0.001$). Furthermore, among patients with penicillin allergy, the hazard ratio for MRSA was 1.84 (95% CI, 1.64 to 2.06) and for *C difficile* 1.37 (95% CI, 1.23 to 1.53). In addition to negative clinical outcomes, observational studies have shown that patients labeled penicillin-allergic acquire higher antibiotic costs compared to those not labeled as such.²

Since approximately 30 million Americans report a history of penicillin allergy, removal of the inaccurate label of penicillin allergy in about 95% of these individuals has public health implications. As the detriments of being labeled penicillin allergic have come to light, efforts to de-label these patients are picking up momentum. For example, the CDC has drawn attention to this important issue with the release of a penicillin allergy factsheet.² Similarly the Choosing Wisely campaign and national allergy societies have highlighted penicillin allergy. Evaluation of penicillin allergy most typically involves penicillin skin testing followed by oral amoxicillin challenge, if the skin test is negative. However, in some

71 clinical scenarios, such as in children with mild reaction histories, there is potential for performing direct
72 oral challenge without prior skin testing.⁵ Whatever the approach to de-labeling is, allergists need to
73 continue to publicize the hazards of penicillin allergy to not just other clinicians, but also directly to the
74 public, whenever possible. Therefore, if a patient ever asks you, “Doctor, I am allergic to penicillin. Is this
75 dangerous?”, the resounding answer should be, “Yes!” – and then proceed to attempt to de-label the
76 allergy.

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