

**Title:** Labeling a patient with penicillin allergy: not a benign practice

**Author:** Tiana Jespersen Nizamic, MD

**Story from the Front Lines:**

A middle-aged woman with history of insulin-dependent type 2 diabetes mellitus and hypothyroidism presented to her primary care provider with a couple days of watery diarrhea, abdominal pain, and nausea. She was diagnosed with *Clostridium difficile* diarrhea via stool PCR and started on oral vancomycin. The patient was recently seen at an Urgent Care for right lower extremity non-purulent cellulitis and prescribed a 5-day course of clindamycin which she just completed last week. Her medical record shows multiple allergies including penicillin and sulfa drugs for which rash is listed as the adverse reaction. On further discussion with the patient regarding her penicillin allergy, she describes being told of “a rash when I was a little kid.” Chart review reveals that she tolerated intravenous cefazolin peri-operatively a few years ago without issues.

**Teachable Moment:**

The widespread use of antibiotics in hospitalized and ambulatory patients has resulted in multiple unique disease entities including antibiotic-associated diarrhea and colitis. Since initially identified in 1978, the prevalence of C difficile-associated diarrhea (CDAD) has continued to increase with almost half a million infections and approximately 29,000 deaths identified in the United States in 2011.<sup>1</sup> Though any antibiotic can predispose to CDAD, 2 large meta-analyses show the most frequently implicated to be clindamycin, fluoroquinolones, broad-spectrum cephalosporins, and penicillins in descending order (OR 16.80-20.43, 5.50-5.65, 4.47-5.50, and 2.70-3.25 respectively).<sup>2,3</sup> Clindamycin, fluoroquinolones, and third-generation cephalosporins are commonly substituted for first-line penicillins in those with an active penicillin “allergy” history, which is the most common drug-class allergy listed in United States medical records seen in up to 10% of patients.<sup>4</sup> However, the vast majority have never undergone confirmatory allergy testing (less than 0.1%) and more than 90% of those with a reported penicillin allergy do not have IgE antibodies when skin testing is performed.<sup>5</sup> Even among those with confirmed allergy, 97% will tolerate cephalosporins.<sup>6</sup> There is widespread but mistaken concern with using first- and second-generation cephalosporins in these patients because of a side chain cross-reactivity hypothesis that has not been validated in large clinical trials including no clinically significant IgE-mediated reaction to beta-lactams sharing side chains (e.g., amoxicillin and cephalexin).<sup>7</sup> Even with the available data, additional assessment of penicillin allergy noted on chart review has not become routine despite noted associations with poor outcomes. A retrospective, matched cohort study of over 51,000 patients showed that hospitalized individuals with penicillin “allergy” averaged 0.59 more total hospital days and had 23.4% more C difficile, 14.1% more MRSA, and 30.1% more VRE infections than expected compared with control subjects.<sup>8</sup> The authors speculate that more than 98% of hospitalized patients with a history of penicillin “allergy” would have negative skin testing results and that performing skin tests routinely would actually save 4 times as much as it would cost to perform the test (assuming negative results in 95% and avoiding only 50% of additional hospital days). Current guidelines suggest clarifying the adverse reaction and referring for skin testing when an IgE-mediated reaction is suspected. This patient’s report of a rash in childhood represents a minor reaction and her risk of developing CDAD could have been significantly reduced by treating non-purulent cellulitis with a cephalosporin rather than clindamycin.

## References:

1. Lessa FC, Winston LG, McDonald LC, Emerging Infections Program CdST. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015;372(24):2369-2370.
2. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrob Agents Chemother*. 2013;57(5):2326-2332.
3. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013;68(9):1951-1961.
4. Macy E. The clinical evaluation of penicillin allergy: what is necessary, sufficient and safe given the materials currently available? *Clin Exp Allergy*. 2011;41(11):1498-1501.
5. del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol*. 2007;98(4):355-359.
6. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy*. 2002;57(12):1151-1158.
7. Macy E, Ngor E. Recommendations for the management of beta-lactam intolerance. *Clin Rev Allergy Immunol*. 2014;47(1):46-55.
8. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol*. 2014;133(3):790-796.