Rostrum

Why Was There Ever a Warning Not to Use Cephalosporins in the Setting of a Penicillin "Allergy"?

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It is now well-established that avoiding β-lactam antibiotics, when they are the drugs of choice, results in significantly worse long-term global outcomes for patients. Much of this avoidable morbidity has been caused by widespread warnings in electronic health care record systems not to use cephalosporins in the setting of penicillin allergy. High rates, up to 1000-fold higher than now seen, of immunologically mediated reactions were associated with early impure penicillin preparations. This instilled a rational fear of β-lactam–associated anaphylaxis in generations of physicians. In the late 1970s, several editorial comments regarding a potential increased risk to patients given cephalosporins who had a history of a penicillin allergy resulted in the warning that became imbedded in the culture of medicine. Over the past 40 years, compelling data have been developed that refute this warning and showed that the risks of avoiding cephalosporins outweighed the benefits. In late 2017, Kaiser Permanente Southern California completely removed all warnings not to use cephalosporins in the setting of a penicillin allergy. The results have recently been published in *JAMA Network Open*. This Rostrum article provides some of the backstory on the establishment and removal of this warning for physicians who trained over the past 30 years. © **2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)**

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INTRODUCTION

Proving a negative may be impossible, as often seems to be the case when trying to change well-entrenched medical orthodoxy, but that has not stopped many people from trying over the past 40 or more years. For decades, it has been taken as fact that cephalosporins should be avoided in the setting of a penicillin allergy, with no valid data supporting the theory that this prohibition improves overall patient safety or global outcomes. Decisions made to improve perceived safety in the short term can have severe, unintended, adverse long-term outcomes. The warning not to use cephalosporins, when they are the antibiotic of choice, in the setting of a penicillin allergy is a classic example of penny-wise and pound-foolish.

Although it was discovered in 1929, penicillin did not go into widespread use until the 1940s. Grossman[1] reminisced on his involvement with one of the first successful uses of penicillin, when his group treated a civilian patient with ß-hemolytic *Streptococcus* sepsis on March 12, 1942. "We discussed what to do with the pungent, brown-red powder. We decided to dissolve it in saline and pass it through an E.K. Seitz [asbestos] filter pad to sterilize it," wrote his coworker, Tager, in 1976. In its pure form, intravenous penicillin is colorless; until they were well-purified in the 1950s, the other materials present in penicillins undoubtedly contributed to many of the early, probably immunologically mediated side effects.

Suchecki[2] reported in 1946 that penicillin use had already been associated with multiple cases of acute urticaria. There appeared to be higher rates of adverse reactions with subsequent exposures. Delayed-onset contact dermatitis occurred after 5% to 25% of topical exposures, but this was less than with topical sulfonamide antibiotics commonly used during that era. This is one reason why we do not currently use topical penicillins. It was subsequently noted that frequent and prolonged exposure to many antibiotics, including penicillins, was associated with immunologic hypersensitivity. Cetinkaya and coworkers[3] reported in 2007 that occult sensitization to penicillin documented by positive penicillin skin test results developed in hospital nurses who had never reported a reaction associated with a therapeutic penicillin exposure. They concluded that those health care workers might be at increased risk for clinically significant hypersensitivity reactions if they were exposed to penicillins administered for therapeutic purposes in the future.

Gordon[4] documented that by 1946, penicillin use was associated with rare cases of serum-sickness-like reactions, occurring at about one in 1500 to 2000 exposures. The onset was typically 2 to 7 days after penicillin therapy ceased, and generally about 10 to 15 days after the start of exposure. Clinical symptoms included joint pain, malaise, fever, and, interestingly, exfoliative dermatitis of the hands. This exfoliative dermatitis would more likely currently be classified as a serious cutaneous adverse reaction (SCAR) rather than as a serum-sickness-like reaction.

Lepper and coworkers[5] reported in 1949 that penicillin use had been associated with two reported deaths from anaphylaxis and one death from a SCAR, exfoliative dermatitis. They also described adverse reaction rates in 1310 sequential penicillin

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Abbreviations used
EHR- Electronic healthcare record
KPNC- Kaiser Permanente Northern California
KPSC- Kaiser Permanente Southern California
SCAR- Serious cutaneous adverse reaction

exposures at a single center, eight of 29 with previous penicillin exposures (27.5%) and 12 of 388 (3.1%) without previous penicillin exposures.

In 1953, Feinberg and coworkers[6] reported on penicillin-associated fatal anaphylaxis. They identified 11 formally reported or anecdotal cases and thought that this represented only a minority of cases. In 1991, the International Rheumatic Fever Study Group reported on 1790 patients receiving 32,340 benzathine penicillin injections, with 2736 patient-years of follow-up. They noted four episodes of anaphylaxis, with one death.[7]

Generations of physicians grew up being taught that penicillins, although generally nontoxic, were associated with potentially high rates of severe acute-onset and delayed-onset allergic reactions, and occasional deaths. The rate of serious adverse reactions was higher with previous exposures. Thus, one avoided these penicillin-associated allergies by never reusing penicillins in individuals with previous reactions, independent of severity.

Only in 1986 did Neftel and coworkers[8] provide insight into what can happen with exposure to penicillins that have been in aqueous phase for a prolonged period. They showed that high-dose intravenous therapy with penicillin-G always results in both the generation of sensitized lymphocytes and anti-penicilloyl IgG antibodies. If penicillin-G was given strictly as a freshly prepared bolus dose, this sensitization was mitigated. In 193 patients, bolus dose intravenous treatment with penicillin-G without special precautions, stored up to 36 hours at 4°C, or given by continuous infusion, led to 8.3% definite, 6.7% probable, and 14.0% possible immunologically mediated adverse reactions. In 116 patients treated exclusively with freshly dissolved penicillin doses, only 0.9% definite, 1.7% probable, and 4.3% possible immunologically mediated reactions were documented. Seven cases of hemolytic anemia and 12 cases of neutropenia were observed in 19 patients in the first group and no such reactions were seen in the second group. Using only freshly prepared single doses prevented most immunologically mediated adverse reactions after high-dose intravenous penicillin-G therapy. The researchers concluded that degradation and transformation products formed in vitro were most likely the causative agents, rather than the native penicillin molecule itself. This may be part of the story explaining what was going on with the pungent brown-red powder that Grossman and Tager used in 1942.[1]

Starting in the mid-1960s, concern was raised that cephalosporin use in patients with a penicillin allergy might be associated with an increased reaction risk.[9] An editorial in the *Journal of the American Medical Association* by Petersdorf[10] in 1969 still stated that cephalothin and cephaloridine could be safely used in individuals with a penicillin allergy. By the mid-1970s, skin and serologic testing showed potential immunologic cross-reactivity between penicillins and first-generation cephalosporins, although clinically significant reactions with therapy were only anecdotally reported, often in small, highly selected case series.[11]

In 1976, Moellering and Swartz[12] reported in the *New England Journal of Medicine* that "all cephalosporins probably should be avoided in patients with a past history of anaphylaxis (or immediate hypersensitivity) to any of the penicillins." They also stated that "whether or not these reactions are due to cross-sensitivity is unknown since penicillin-allergic patients have an increased rate of reactivity to immunologically unrelated drugs."

Petz[13] remarked in 1978 that that patients with a history of penicillin allergy appeared to have an increased incidence of reactivity to cephalosporins. He said that it was impossible at the time to determine to what extent this finding resulted from immunologic cross-reactivity because penicillin-allergic patients also had an increased incidence of apparent acute-onset hypersensitivity reactions to drugs immunologically unrelated to penicillins. Petz also commented on recent evidence of specific immune responses to cephalosporins that indicated independently acquired hypersensitivity rather than immunologic cross-reactivity in some patients.[13]

Because of the comments by Moellering and Swartz[12] and Petz,[13] and despite the important caveats noted earlier, global avoidance of all cephalosporins in the setting of any penicillin allergy became imbedded in the culture of medicine. Around this time, a myth also developed of 10% cross-reactivity between penicillin and cephalosporins, with no supporting population-based challenge data.[14]

No population-based challenge data have ever been presented showing that cephalosporin-associated reactions were more significantly common in individuals with a penicillin allergy over the expected increase rate of antibiotic intolerances seen in individuals with other preexisting reports of any other antibiotic intolerance. No population-based data have ever been presented showing that avoiding cephalosporins in the setting of a penicillin allergy resulted in better global outcomes. No population-based data have ever been presented showing that using cephalosporins in the setting of a penicillin allergy resulted in worse global outcomes. Anecdotal cases of patients with an allergy to penicillin who have died of cephalosporin-associated anaphylaxis have often driven the narrative. Essentially, the fear of anaphylaxis has caused the unintended result of real but delayed harm of globally worse clinical outcomes for generations of patients. We now know there is significant morbidity associated with the use of non-ß-lactams when ß-lactams are the antibiotics of choice.[15-20]

Pushback on this orthodoxy soon began. In 1987, Saxon and coworkers[21] at the University of California, Los Angeles reported that their results of in vivo challenges of patients with IgE to penicillin suggested that the incidence of reactivity to cephalosporins in patients allergic to penicillin was much less than 10%.

They challenged 62 penicillin skin test−positive subjects with a therapeutic regimen of a clinically indicated parenteral cephalosporin antibiotic beginning on the same day as the positive skin test result. They documented only one benign delayed onset reaction starting 24 hours after the exposure (1.6%).

Knowing accurately the background population-based incidence of new penicillin and cephalosporin allergy reports, anaphylaxis, and SCARs is essential when evaluating whether a warning to avoid the use of cephalosporins in the setting of a penicillin allergy could improve patient safety. In 2009, we reported on antibiotic allergy incidence and prevalence rates in 411,543 patients cared for by Kaiser Permanente in San Diego County.[22] Population-based data were collected from our newly

active electronic health care record (EHR) system, which for the first time contained all outpatient, inpatient, and pharmacy data for all of 2007 through the first half of 2008. We saw that a new penicillin allergy was recorded in 1.45% of females and 1.11% of males exposed to penicillins within 6 months of treatment. The rate after therapeutic cephalosporin exposures were 1.08% for females and 0.60% for males. Antibiotics with the highest rate of new allergy reports were sulfonamides (3.42% for females and 2.23% for males). Therefore, when Saxon and coworkers[21] noted that 1.6% of penicillin skin test−positive individuals had a new cephalosporin allergy event, this was only about twice the rate seen in random patients, as we found in 2009.

In 2012, we reported on the incidence rate of new antibiotic allergies, independent of any actual antibiotic exposure, recorded in the EHRs of 2,375,424 Kaiser Permanente Southern California (KPSC) health plan members who had at least one health care visit and at least 11 months of health care coverage during 2009.[23] We found that a new penicillin allergy report was entered into the EHR of about 0.5% of health plan members during 2009, compared with about 0.2% who received a new cephalosporin allergy report, about 0.3% who received a new sulfonamide antibiotic allergy report, and about 0.5% who received a new opiate allergy report. Many of these individuals had no penicillin or cephalosporin exposures during 2009. The key finding was that the incidence rate of all new antibiotic allergy reports in individual patients was higher in females and rose dramatically with the total number of unrelated drug allergies reported in those patients. Individuals with the highest number of reported drug allergies also used the most overall drugs, had more hospital days, and more overall health care visits.

In 2020, we reported on penicillin use and penicillin-associated adverse drug reactions occurring in 6,144,422 KPSC members who had at least one health care visit from January 1, 2009 through December 31, 2017, accounting for 37,387,313 years of health plan coverage.[24] Mean age of the cohort was 33.6 ± 21.1 years and 52.2% were females. They had a total of 5,617,402 oral penicillin exposures, and a new penicillin allergy was reported within 30 days in 0.74% after each therapeutic exposure. Only 22 confirmed anaphylaxis cases (one in 255,320) were associated with oral exposures. This cohort also had 370,478 parenteral penicillin exposures, with new penicillin allergy reported in 0.85%. There were only three confirmed anaphylaxis cases (one in 123,792) with parenteral exposures. There were no deaths from anaphylaxis. Thus, only one in 1543 new allergy reports after oral penicillin exposures (0.065%) were confirmed to be anaphylaxis and only one in 1030 new allergy reports after parenteral exposures (0.097%) were confirmed to be anaphylaxis. There were no cases of SCARs uniquely associated with only the use of a penicillin.

We published a similar analysis of cephalosporin use and cephalosporin-associated adverse drug reactions in 2015 after reviewing the EHRs of 622,456 KPSC health plan members exposed to 901,908 courses of oral cephalosporins and 326,867 members exposed to 487,630 courses of parenteral cephalosporins between January 1, 2010 and December 31, 2012.[25] New cephalosporin allergies were more frequent among women exposed to cephalosporins (0.56%; 95% confidence interval [CI], 0.54% to 0.57%) compared with men (0.43%; 95% CI, 0.41% to 0.44%) per course ($P < .0001$). Cephalosporin-associated anaphylaxis was much rarer than often previously assumed or reported. We confirmed that cephalosporin-associated anaphylaxis occurred with only five oral exposures (95% CI, 1:1,428,571-1:96,154) and eight parenteral exposures (95% CI, 1:200,000-1:35,971) ($P = .0761$) and there were no deaths from anaphylaxis. We did not find an increased rate of cephalosporin-associated anaphylaxis in the subgroup of 65,915 penicillin-allergic patients given 127,125 courses of cephalosporins compared with individuals with no drug allergies. There were only three documented cases of cephalosporin-associated SCARs (95% CI, 0-1 in 217,291) and all were associated with the use of another antibiotic at the same time as cephalosporin, which was likely the cause. We noted that cephalosporins were the most commonly used antibiotic family in individuals with a penicillin allergy in our health plan, with no testing or challenges, despite an active warning in our EHR not to use cephalosporins when a penicillin allergy was reported.

In 2009, we reported that the rate of positive penicillin allergy evaluations had been falling over the past 20 or more years in our population, probably associated with less exposures to aged parenteral penicillins.[26] In 2011, we saw that that even in individuals with a history of verified penicillin allergy, based on positive penicillin skin test results, cephalosporins were widely used and tolerated with adverse reactions rates not significantly different from those in individuals with any other antibiotic allergy.[27] As expected, sulfonamide antibiotics had the highest new allergy report rate in individuals with a penicillin, cephalosporin, or any other antibiotic allergy.

By 2016, there were good data to support the following arguments. It had never been shown that avoiding cephalosporins in the setting of a confirmed or unconfirmed penicillin allergy resulted in improved overall outcomes. Penicillin- and cephalosporin-associated anaphylaxis and SCARS were extremely rare. Cephalosporin-associated anaphylaxis was not more likely in individuals with a penicillin allergy. The rate of new cephalosporin allergies in individuals with a penicillin allergy was no higher than expected in individuals with any other antibiotic allergy. The warning not to use cephalosporins in the setting of a penicillin allergy was widely ignored. There was good evidence that avoiding β-lactams, when they were the antibiotics of choice, resulted in worse overall outcomes.

In December 2017, the physicians of the Southern California Permanente Medical Group, who provide all clinical care to members of KPSC, completely removed the warning not to use cephalosporins when a penicillin allergy was reported from their EHR system. The same information was presented, albeit less effectively, to physicians of the Permanente Medical Group, who provide all clinical care to members of Kaiser Permanente Northern California (KPNC), and they elected to retain the warning. This had the unintended effect of setting up a large cluster-randomized prospective trial using two fairly well-matched large population-based health care systems, one with the warning in place and the other without the warning.

Subsequent to our removal of the warning, Jeffres and coworkers[28] reported that there was a very low legal risk when appropriately prescribing clinically indicated cephalosporins to individuals with confirmed or unconfirmed penicillin allergies.

This was essentially the perfect study design to determine at a population level whether having a warning to avoid cephalosporins, in the setting of a confirmed or unconfirmed penicillin allergy, resulted in different overall outcomes. The health care system with the warning in place should have fewer negative outcomes if the warning were justified.

The results of this experiment was recently published in *JAMA Network Open*.[29] Briefly, the study population included 4,206,480 patients in KPSC and KPNC exposed to 10,652,014 courses of therapeutic systemic antibiotics, approximately half of which were in the pre and post periods. Cephalosporin use among patients with a penicillin allergy in KPSC increased 51% in the post period (ratio of odds ratio = 1.47; 95% CI, 1.38-1.56). At the course level, there was no significant difference in the incidence of anaphylaxis, new antibiotic allergies, or treatment failures. At the patient level, there was no difference in all-cause mortality, hospital days, or new drug-resistant infections between KPSC and KPNC. The warning not to use cephalosporins in the setting of a penicillin allergy did not improve overall outcomes and did not worsen overall outcomes.

Removing the warning not to use cephalosporins in the setting of a penicillin allergy is a simple and rapidly implementable systems-level intervention to improve antibiotic stewardship. It was associated with more appropriate antibiotic prescribing without negative consequences for patients. These findings may encourage other systems to consider similar actions. Removing the warning did not significantly reduce known morbidities associated with an unconfirmed penicillin allergy, probably because the warning was so widely ignored, even in KPNC, where it remained.[29] Penicillin allergy de-labeling still needs to be aggressively pursued to address this excess and avoidable morbidity.[30,31]

We recently reported on a subcohort of over 15,000 individuals from the previously mentioned study, who specifically described an ampicillin, cephalexin, or cefaclor allergy and were treated with ampicillin, cephalexin, cefaclor, or trimethoprim-sulfamethoxazole, and compared their outcomes with a control group of over 1.2 million individuals without a ampicillin, cephalexin, or cefaclor allergy, who were treated with ampicillin, cephalexin, cefaclor, or trimethoprim-sulfmathoxazole.[32] The rates of newly reported ampicillin, cephalexin, cefaclor, or trimethoprim-sulfamethoxazole allergies were about twofold higher in the cohort with the preexisting ampicillin, cephalexin, or cefaclor allergy, indicating no clinically significant increased risk with the shared side chain.

I recommend that all health plans remove all warnings not to use cephalosporins or other β-lactams, such as monobactams and carbapenems, in individuals with both confirmed penicillin allergy and unconfirmed penicillin allergy from their EHR systems. It is still unclear whether using a β-lactam with the same side chain as an implicated β-lactam leads to a higher risk for clinically significant adverse outcomes based on currently available challenge data, but the preponderance of the data suggests that it is typically safe and leads to better outcomes.[21,25,27,33] I currently recommend that cephalosporin warnings trigger only for attempted readministration of the same cephalosporin. The extremely low risk of anaphylaxis is greatly outweighed by the significant risk for treatment failure or other side effect when the cephalosporin of choice is not used.

An unverified penicillin allergy remains a significant public health problem, and all individuals with a penicillin allergy should have the allergy confirmed or removed.[31,33] Less than 5% of individuals with a history of penicillin allergy are confirmed to be allergic by properly performed penicillin allergy testing.[33] A direct oral amoxicillin challenge with a single therapeutic dose is indicated in penicillin-allergic individuals with low-risk histories to confirm acute tolerance.[34] Cephalosporins and other β-lactams, even those sharing exact side chains, are safely used, even in individuals with confirmed penicillin allergy, and are widely and appropriately used in individuals with an unconfirmed penicillin allergy.[29,34]

REFERENCES

1. Grossman CM. The first use of penicillin in the United States. Ann Intern Med 2008;149:135-6.
2. Suchecki AI. Allergic reactions to penicillin. BMJ 1946;2:938-40.
3. Cetinkaya F, Ozturk AO, Kutluk G, Erdem E. Penicillin sensitivity among hospital nurses without a history of penicillin allergy. J Adv Nurs 2007;58:126-9.
4. Gordon EJ. Delayed serum sickness reaction to penicillin. JAMA 1946;131:727-30.
5. Lepper MH, Dowling HF, Robinson JA, Stone TE, Brickhouse RL, Caldwell ER, et al. Studies on hypersensitivity to penicillins. I. incidence of reactions in 1303 patients. J Clin Invest 1949;28:826-31.
6. Feinberg S, Feinberg AR, Moran CF. Penicillin anaphylaxis, nonfatal and fatal reactions. JAMA 1953;152:114-9.
7. International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. Lancet 1991;337:1308-10.
8. Neftel KA, Walti M, Schelthess HK, Gubler J. Adverse reactions following intravenous penicillin-G relate to degradation of the drug in vitro. Klin Wochenscher 1986;62:25-9.
9. Thoburn R, Johnson JE III, Cluff LE. Studies on the epidemiology of adverse drug reactions IV. The relationship of cephalothin and penicillin allergy. JAMA 1966;198:111-4.
10. Petersdorf RG. Penicillin. JAMA 1969;209:1520-1.
11. Assem ESK, Vickers MR. Tests for penicillin allergy in man. Immunology 1974;27:255-69.
12. Moellering RC Jr, Swartz MN. Drug therapy. The newer cephalosporins. N Engl J Med 1976;294:24-8.
13. Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. J Infect Dis 1978;137(suppl):S74-9.
14. Herbert ME, Brewster GS, Lanctot-Herbert M, Medical myth. Ten percent of patients who are allergic to penicillin will have serious reactions if exposed to cephalosporins. West J Med 2000;172:341.
15. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. J Antimicrob Chemother 2015;70:2382-8.
16. Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomized controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents 2016;48:1-10.
17. Pool C, Kass J, Spivack J, Nahumi N, Khan M, Babus L, et al. Increased surgical site infection rates following clindamycin use in head and neck free tissue transfer. Otolaryngol Head Neck Surg 2016;154:272-8.
18. Koliscak LP, Johnson JW, Beardsley JR, Miller DP, Williamson JC, Luther VP, et al. Optimizing empiric antibiotic therapy in patients with severe β−lactam allergy. Antimicrob Agents Chemother 2013;57:5918-23.
19. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding β-lactams in patients with β-lactam allergies. J Allergy Clin Immunol 2016;137:1148-53.
20. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis 2018;66:329-36.
21. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204-15.
22. Macy E, Poon K-YT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med 2009;122:778.e1-7.
23. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. Ann Allergy Asthma Immunol 2012;108:88-93.
24. Liang EH, Chen LH, Macy E. Adverse reaction associated with penicillins, carbapenems, monobactams, and clindamycin: a retrospective population-based study. J Allergy Clin Immunol Pract 2020;8:1302-1313.e2.
25. Macy E, Contreras R. Adverse reactions associated with oral and parenteral cephalosporin use: a retrospective population-based analysis. J Allergy Clin Immunol 2015;135:745-752.e5.
26. Macy E, Schatz M, Lin C, Poon KWT. The falling rate of positive penicillin skin tests from 1995 to 2007. Perm J 2009;13:12-8.

27. Macy E, Ho NJ. Adverse reactions associated with therapeutic antibiotic use after penicillin skin testing. Perm J 2011;15:31-7.
28. Jeffres M, Hall-Lipsy E, King ST, Cleary J. Systematic review of professional liability when prescribing B-lactams for patients with a known penicillin allergy. Ann Allergy Asthma Immunol 2018;121:530-6.
29. Macy E, Crawford W, Nguyen M, Adams J, Davis A, McGlynn E, et al. Removing the warning not to use cephalosporins in individuals with a penicillin allergy: the effect on cephalosporin allergy and anaphylaxis incidence. JAMA Netw Open 2021;4:e218367.
30. 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;133:790-6.
31. Macy E, Shu Y-H. The effect of penicillin allergy testing on future healthcare utilization: a matched cohort study. J Allergy Clin Immunol Pract 2017;5:705-10.
32. Macy E, McCormick T, Adams J, Crawford W, Nguyen M, Davis A, et al. Population-based incidence of new ampicillin, cephalexin, cefaclor, and sulfonamide antibiotic "allergies" in exposed individuals with and without preexisting ampicillin, cephalexin, or cefaclor "allergies. J Allergy Clin Immunol 2021;147:AB8.
33. Shenoy E, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019;321:188-99.
34. Vyles D, Macy E. Self-reported beta-lactam intolerance: not a class effect, dangerous to patients, and rarely allergy. Expert Rev Anti Infect Ther 2019;17:429-35.