CJC Open 4 (2022) 695–700

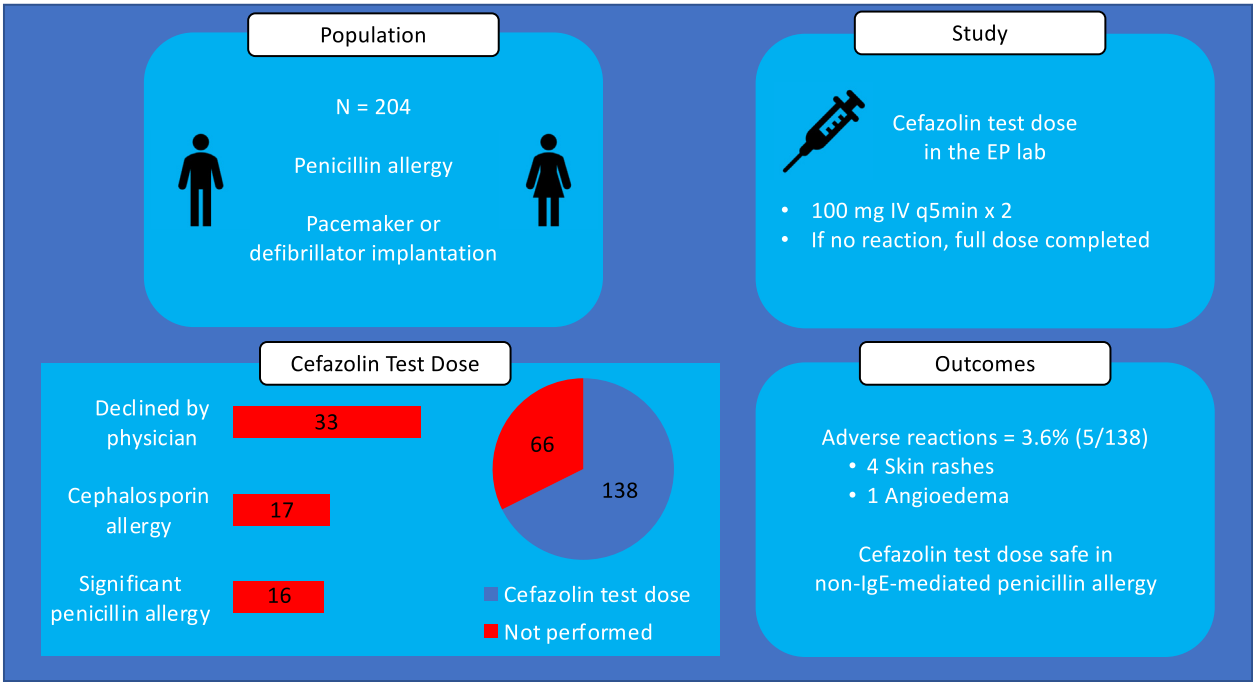
Original Article

Safety of Cefazolin Test Dose in Patients With Penicillin Allergy Just Prior to Cardiac Device Implantation: A Single-Centre Experience

Jean-François Sarrazin, MD,[a] Jamal Laaouaj, MD,[a] François Philippon, MD,[a] Marina Sanchez, PhD,[a] Philippe Gervais, MD,[b] Jean Champagne, MD,[a] Christian Steinberg, MD,[a] Isabelle Nault, MD,[a] Karine Roy, MD,[a] Benoît Plourde, MD,[a] Louis Blier, MD,[a] and Gilles O'Hara, MD[a]

[a] *Department of Cardiology, Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Québec City, Canada*

[b] *Department of Infectious Disease, Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Québec City, Canada*



ABSTRACT

Background: Cephalosporins are the cornerstone of cardiac device infection prophylaxis. Owing to fears of cross-reactivity, penicillin-allergic patients are exposed to potentially more-toxic drugs, with decreased efficacy. We evaluated the safety of a cefazolin test dose (CTD) in self-reported penicillin-allergic patients.

Methods: In this single-centre study, we evaluated consecutive patients with chart documentation of penicillin allergy undergoing cardiac

RÉSUMÉ

Contexte : Les céphalosporines sont la pierre angulaire de la prophylaxie des infections des dispositifs cardiaques. En raison du risque appréhendé de réactivité croisée, les patients allergiques à la pénicilline se trouvent exposés à des médicaments potentiellement plus toxiques, qui s'avèrent aussi moins efficaces. Nous avons évalué l'innocuité d'une dose d'essai de céfazoline chez des patients qui s'étaient dits allergiques à la pénicilline.

https://doi.org/10.1016/j.cjco.2022.04.007

device implantation, over a 2-year period. A CTD was performed if no cephalosporin allergy or severe anaphylactic reaction to penicillin had been documented. Patients were given 2 doses of 100 mg IV cefazolin, and if no allergic reaction occurred after 5 minutes, the full dose (1800 mg) was administered in the electrophysiology laboratory just before the implantation procedure.

Results: A total of 2200 patients were included. The frequency of reported penicillin allergy was 9.3% (n = 204). In 80% of cases, the type of allergic reaction was not reported in medical notes or was unknown by the patient. A CTD was performed in 67.6% of patients with a penicillin allergy (n = 138). A total of 5 adverse events occurred (3.6% of patients [95% confidence interval, 1.1%-6.1%]) — 4 skin rashes and 1 tongue edema. These 5 patients became asymptomatic after antihistaminic and corticosteroid IV treatment. Even if the test dose was negative, 79% of patients also were administered vancomycin before the procedure, as it requires a 1-hour infusion prior to the CTD in the implantation procedure room.

Conclusion: A CTD in most penicillin-allergic patients appears to be safe and allows its use per recommended guidelines.

Méthodologie : Dans cette étude monocentrique, nous avons suivi pendant deux ans des patients consécutifs dont le dossier médical faisait état d'une allergie à la pénicilline et chez qui un dispositif cardiaque devait être implanté. Une dose d'essai de céfazoline a été administrée aux patients sans antécédents documentés d'allergie aux céphalosporines ou de réaction anaphylactique sévère à la pénicilline. Deux doses de 100 mg de céfazoline ont été administrées par voie intraveineuse. En l'absence de réaction allergique après cinq minutes, les patients recevaient la dose complète (1 800 mg) au laboratoire d'électrophysiologie juste avant l'implantation du dispositif cardiaque.

Résultats : Au total, 2 200 patients ont été inscrits à l'étude. Le taux de signalement de l'allergie à la pénicilline était de 9,3 % (n = 204). Dans 80 % des cas, le type de réaction allergique n'a pas été précisé dans les notes médicales ou était inconnu du patient. Une dose d'essai de céfazoline a été administrée à 67,6 % des patients allergiques à la pénicilline (n = 138). Au total, cinq événements indésirables se sont produits (3,6 % des patients [intervalle de confiance à 95 % : 1,1-6,1 %]) – quatre éruptions cutanées et un œdème de la langue. Les cinq patients touchés par ces événements sont devenus asymptomatiques après avoir reçu un antihistaminique et un corticostéroïde par voie intraveineuse. Même en l'absence de réaction allergique à la dose d'essai, 79 % des patients ont reçu de la vancomycine avant l'intervention, cet agent devant être administré par perfusion durant une heure avant la dose d'essai de céfazoline dans la salle d'intervention.

Conclusion : Chez la plupart des patients allergiques à la pénicilline, une dose d'essai de céfazoline semble sans danger et permet d'avoir recours à ce médicament conformément aux lignes directrices.

Cardiac implantable electronic device (CIED) infection is a significant complication associated with a high level of morbidity and mortality. The pathophysiology of CIED infection is often related to contamination by local skin pathogens at the time of device implantation.[1] Then, the infection can spread from the pocket along the electrodes, causing bacteremia and lead-related or valvular endocarditis.

The incidence of CIED infection varies from 1% to 3% in North American and European countries.[2-4] This rate has been increasing because CIED indications and use of cardiac resynchronization therapy (CRT) are expanding to a population with more risk factors for infection.[5,6]

Aside from application of optimal surgical technique, preoperative intravenous (IV) antibiotic administration remains one of the most important strategies for prevention of postoperative infection. Cefazolin, a first-generation cephalosporin, is supported by guidelines, as it effectively combats most common skin pathogens associated with device infection.[7] Recent data show that in higher-risk populations, the use of either an incremental antibiotic strategy[6] or an antibiotic envelope also may reduce infection risk.[8]

Penicillin Allergy

Penicillin and cephalosporins are the most widely used antibiotics. Many patients say they have an allergy to penicillin, but it is confirmed as a severe allergy in only a few patients.[9] IgE-mediated reactions occur immediately (within 1 hour) and manifest as urticaria, angioedema, bronchospasm, and/or anaphylaxis, as opposed to non-IgE-mediated reactions, which occur days to weeks after exposure (delayed reaction). In patients with IgE-mediated penicillin hypersensitivity, the level of cross-reaction to cephalosporins varies between 1% and 10%. A review examining the level of positive response to a cephalosporin challenge estimated it to be 4.4%.[10]

Given these findings, administration of cephalosporins to penicillin-allergic patients poses some concern. Because of the fear of cross-reactivity, the most common approach taken for penicillin-allergic patients is to select an antibiotic that does not contain the ß-lactam ring, such as vancomycin or clindamycin. However, reduced effectiveness, higher cost, and increased risk of side effects are major drawbacks of this strategy.

The aim of the current study is to report the frequency of penicillin allergy in a real-world patient population undergoing CIED implantation and to establish the safety of administering a pre-procedure incremental cefazolin test dose

Received for publication February 1, 2022. Accepted April 22, 2022.

Ethics Statement: The protocol was approved by the institutional review committee (CER 22113).

Corresponding author: Dr Jean-François Sarrazin, Institut universitaire de cardiologie et de pneumologie de Québec, 2725 chemin Sainte-Foy, Quebec, QC G1V 4G5, Canada. Tel.: +1-418-656-4598; fax: +1-418-656-4581.

E-mail: jean-francois.sarrazin@criucpq.ulaval.ca

See page 699 for disclosure information.

Table 1. Clinical characteristics in penicillin (PNC)-allergic patients (n = 204)

Characteristic	Value for PNC-allergic patients
Age, y	72 ± 7
Male	97 (47.5)
BMI, kg/m^2	27.5 (6.1)
Hypertension	146 (71.6)
Diabetes	44 (21.6)
Chronic kidney disease (MDRD GFR < 60 mL/min)	81 (39.7)
Anticoagulation	100 (49.0)
NOAC	34 (16.6)
Warfarin	65 (31.9)
Others	1 (0.5)
Antiplatelet therapy	132 (64.7)
Immunosuppressed patients	9 (4.4)
Temporary pacing	4 (2.0)
Preoperative antibioprophylaxis	204 (100)
Cefazolin alone	28 (13.7)
Vancomycin alone	66 (32.4)
Vancomycin and cefazolin	109 (53.4)
Clindamycin alone	1 (0.5)
First procedure (pacemaker or defibrillator)	140 (68.6)
Generator replacement	41 (20)
Device upgrade or lead revision	23 (11.3)
Procedure duration, min	40 ± 26

Values are mean ± standard deviation, or n (%).

GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NOAC, non−vitamin K oral anticoagulation.

followed by full-dose administration in those patients without previous skin testing.

Methods

We evaluated all consecutive patients referred for a CIED procedure over a 2-year period at a single, university tertiary-care centre. Eligible procedures included new device implantation, generator replacement, and upgrade/lead-revision procedures. During this period, penicillin-allergic patients were defined as those with a self-reported pencillin allergy or those with a chart and/or pharmacy-labelled penicillin allergy. After chart screening and clinical assessment was performed, an IV cefazolin test dose (CTD) was administered to penicillin-allergic patients, unless it was refused by the attending physician. Exclusions included patients with previous anaphylaxis or severe respiratory manifestation to penicillin administration and those with confirmed allergy to cephalosporins. Even patients with a mild cephalosporin allergy were excluded, except for 7 patients with unspecified allergy. No antibacterial envelope was used in this study. The CTD consisted of the administration of 100 mg IV cefazolin, under medical supervision in the electrophysiology laboratory, with the same dose repeated 5 minutes later if no reaction occurred, and then followed an additional 5 minutes later by 1800 mg of cefazolin, completing the full dose. The protocol was approved by the institutional review committee (CER 22113).

Data collection

In penicillin-allergic patients, the collected data included the type of penicillin allergy declared, CTD administration, clinical response to the CTD, and all perioperative antibiotics received. Other data were also collected, such as anticoagulation and antiplatelet use, use of immunosuppression, presence of chronic kidney disease, temporary pacing, and duration and type of the procedure.

Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and are expressed as mean ± standard deviation (SD) or median (interquartile range). Categorical variables are expressed as number and percentage and were analyzed using the Fisher exact test or the χ^2 test. Quantitative data were compared using the Student t test or the Mann-Whitney U test, as appropriate. To ascertain the expected true proportion of adverse reactions related to the CTD, a Bayesian estimation was performed using a likelihood model with a Bernoulli distribution, Jeffreys prior for normal distribution, and random walk Metropolis-Hastings sampling. A P value of < 0.05 was considered statistically significant. All statistical analysis was conducted using Stata 14.1 software (StataCorp, College Station, TX).

Results

Over a 2-year period, 2200 patients underwent a CIED procedure. In 204 patients (9.3%), the medical record reported a penicillin allergy. Characteristics of the patients with a penicillin allergy are shown in Table 1. Their mean age was 72 ± 7 years, and more were female (52.5% vs 33.0%; $P < 0.001$). The type of allergic reaction was documented in 20.1% of cases (41 of 204). For those reported, the type of reaction was a skin rash in 53.7% (22 of 41), angioedema in 29.3% (12 of 41), anaphylaxis in 2.4% (1 of 41), and other manifestations in 14.6% (6 of 41). Having a penicillin allergy documented on the medical chart was associated with having at least one other drug allergy in 42.2% of patients (86 of 204), including 16 possible reactions to cephalosporins, 49 reactions to a different class of antibiotics, 23 reactions to iodine, 16 reactions to nonsteroidal anti-inflammatory drugs, and 24 reactions to narcotics.

The CTD was administered in 67.6% of penicillin-allergic patients (138 of 204). A CTD was not administered in 66 patients — 7.8% of patients (16 of 204) because of significant prior allergic reaction to penicillin (anaphylaxis = 1; respiratory distress = 2; significant rash = 3; angioedema = 10); 8.3% of patients (17 of 204) because of a previous cephalosporin allergic reaction; and because it was declined by the treating physician in 33 patients (16.1%), many of whom had several concomitant allergies.

Five patients (3.6% [95% confidence interval {CI}, 1.1%-6.1%]) experienced an adverse event following the CTD — 4 had skin rashes, and 1 had angioedema. The reaction occurred after the first dose of 100 mg in 2 patients, after the second dose

Table 2. Adverse clinical events in penicillin-allergic patients (n = 204)

Complication	n (%)
Hematoma	7 (3.4)
Lead dislodgement	4 (2.0)
Infection	3 (1.5)

of 100 mg in 2 other patients, and during the infusion, but prior to completion of the full dose of cefazolin, in the remaining patient. The full dose of cefazolin was not completed in these 5 patients. All 5 were successfully treated with IV corticosteroids and antihistamine drugs, with no further adverse events. No anaphylactic reaction occurred, and no prolonged hospital stay or intensive-care-unit stay was required.

In CTD-negative patients, all patients received their full dose of cefazolin, but only 21.1% of patients (28 of 133) received cefazolin alone, as antibiotic prophylaxis. No delayed allergic reactions occurred after a negative CTD. The final IV antibiotic regimen administered was cefazolin alone in 28 of 204 patients (13.7%), vancomycin alone in 66 of 204 (32.4%), both in 109 of 204 (53.4%), and clindamycin in 1 patient who was allergic to penicillin and vancomycin. Even if the test dose was negative, 79% of patients also received vancomycin before the procedure, because it requires a 1-hour infusion and had to be started prior to the CTD, which was administered in the procedure room under medical supervision.

Complications in patients who had a penicillin allergy are reported in Table 2. During the follow-up, no infection occurred in the cefazolin-alone group; and 3 infected patients required device and lead removal in the vancomycin-alone group (not statistically significant, $P = 0.55$).

Discussion

In this study, we found the following: (i) the frequency of presumptive penicillin allergy in patients referred for a CIED procedure was 9.3%; (ii) the administration of a CTD in patients with a non-IgE-mediated penicillin allergy is safe; and (iii) a CTD can help confirm the absence of cross-reactivity to cefazolin and allow its use in the future.

The observed frequency of reported penicillin allergy in our population was 9.3%, which is consistent with the level reported previously.[11] A CTD was performed in 67.6% of penicillin-allergic patients. A CTD was not performed in several patients, including 16.1% of patients who had either a prior significant allergic reaction to penicillin or a documented cephalosporin reaction. Given that the CTD was given at the discretion of the treating physician, some patients did not receive it. Our study confirmed that the CTD is safe, with only 4 skin rashes and 1 angioedema reported, and no cases of anaphylaxis.

The rate of confirmed penicillin-allergic patients is certainly overestimated, as pointed out by Pichichero.[12] Adding to the confusion related to defining "an allergic reaction," criteria are often vague, especially when the previous reaction was not severe, and allergy often is not differentiated from "intolerance." Many patients labeled as having a penicillin allergy had non-immunologic side effects, such as diarrhea, vomiting, or a nonspecific rash. Cook et al.[13] reported that the true rate of contraindication to penicillin was 0.9%, as determined by skin tests in the cardiac surgery population.

Conducting a thoughtful and detailed history is a key element in the context of screening for ß-lactam allergies, and it often determines the likelihood of identifying a true underlying allergy.[14] In the absence of a detailed history and a critical evaluation of the allergic reaction, many patients will be mislabeled as allergic to ß-lactam antibiotics. Despite the importance of the allergy history, incomplete documentation of allergic reactions is widespread, occurring in up to 66% of patients.[15] In our work, we found incomplete information about penicillin allergy in an even higher percentage of patients (80%). When assessing a patient with a drug allergy, documentation of the date and timing of the allergic reaction, the type of hypersensitivity, the treatment given, and the tolerance to other similar drugs is important. In most clinical scenarios, a patient who had a severe reaction will remember this if asked.

Physicians are often not well prepared to care for penicillin-allergic patients immediately before a surgical intervention. Indeed, Blumenthal et al.[16] reported that physicians, residents, and nurse practitioners had limited prior drug-allergy education. Moreover, the implementation of an inpatient antibiotic standard regimen for patients with a penicillin or cephalosporin allergy was associated with an almost 7-fold increase in the number of test doses to ß-lactams, without an increase in adverse drug reactions.[17] Given the fear of cross-reactivity, the existence of a protocol in our centre clearly encouraged physicians to perform the CTD in most penicillin-allergic patients. Our results were then used to standardize the CTD in all patients with no known angioedema to penicillin.

The 2007 Society of Thoracic Surgeons practice guidelines recommend, for non-IgE-mediated reactions to penicillin (such as a simple rash), the use of cephalosporin administration (class I, level of evidence B), without any test dose.[18] In IgE-mediated reactions, vancomycin administration or skin-test challenges are recommended prior to readministration of cephalosporins (class I, level A). Current CIED guidelines lack clear recommendations on this issue.[19] However, performing a CTD can reassure physicians in treating non-IgE-mediated penicillin-allergic patients and decrease use of vancomycin as a single-antibiotic prophylaxis in this population.

The additional benefit from performing a CTD is the confirmation that no cephalosporin allergy is present and that its administration for other medical conditions is safe. Li et al.[20] reported that prescription of non-ß-lactam antibiotics in patients with an equivocal history of penicillin allergy resulted in 1.82- to 2.58-fold higher costs, compared to administration of standard first-line antibiotics.

The alternative for CIED infection prophylaxis in cefazolin-allergic patients is vancomycin. In our study, we found 3 infections in the group of 66 patients for whom vancomycin alone was administered, and 0 infections in the 28 patients in the cefazolin-alone group, a difference that is not statistically significant, although a sample-size effect cannot be excluded. Bolon et al.,[21] in a meta-analysis of 7 randomized trials, reported no difference between glycopeptides and ß-lactam for the reduction of surgical-site infection at 30 days. However, in a subanalysis, ß-lactams were found to be superior to glycopeptides for prevention of chest infection, and they approached superiority for prevention of deep chest infections caused by gram-positive bacteria. Glycopeptides were superior for prevention of surgical-site infections caused by methicillin-resistant gram-positive bacteria.[22]

Skin testing is usually recommended to assess penicillin allergy. Some authors have reported the value of using preoperative skin testing to reduce vancomycin use in cardiac[13] or orthopedic[23] surgeries. However, Phillips et al. reported that the use of vancomycin in patients with a suspected history of

IgE-dependent allergy in cardiovascular surgery prophylaxis was cost effective, and safer than performing a penicillin skin test or giving cefazolin to all penicillin-allergic patients.[24]

Beltran et al.[25] reported in a pediatric surgery prophylaxis study that the administration of cephalosporins in cases of non-IgE-mediated hypersensitivity was safe. Among 123 penicillin-allergic patients who received cefazolin, only 1 case of non-anaphylactic reaction occurred. A recent meta-analysis found that cross-reactivity between penicillin and cefazolin was rare, including in the subgroup of surgical patients.[26]

The guidelines published in 2015 for the diagnosis of drug-hypersensitivity reaction[27] reported that a drug-provocative test is indicated to exclude hypersensitivity when the history is unclear or to exclude cross-reactivity with related drugs. However, clinical practice often does not allow time to perform the test electively before CIED implantation. Using a CTD is cost effective and clinically applicable, and such a strategy is needed in view of the clinical importance of CIED infection prevention..

Limitations

Our study has some limitations. The administration of the CTD was not randomized, but rather was at the discretion of the treating physician. Second, the identification of penicillin-allergic patients was based on either self-report or documentation in the medical records. Patients were not screened with a skin test to confirm their penicillin allergy, a common problem reported in other trials as well. The duration of CTD observation was limited so that it could be performed within a reasonable time prior to the intervention, and no delayed reaction was observed. The overall rate of CIED infection at 30 days was too small to compare infection rates among different antibiotic strategies.

Conclusions

Reported penicillin-allergic patients represent 9.3% of a contemporary population undergoing CIED procedures. A CTD in non-IgE-mediated penicillin-allergic patients appears to be safe and useful in decreasing the use of vancomycin alone in this population, but it should be balanced against the risk and safety of administering other antibiotics. A standard operating procedure for CTD administration can be applied systematically; in this way, a CTD is safe and can prevent suboptimal antibiotic prophylaxis before CIED procedures in patients without confirmed cephalosporin allergy, previous anaphylaxis, or severe respiratory distress to penicillin.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Da Costa A, Lelièvre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. Circulation 1998;97:1791-5.
2. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. J Am Coll Cardiol 2011;58:1001-6.
3. Ahsan SY, Saberwal B, Lambiase PD, et al. A simple infection-control protocol to reduce serious cardiac device infections. Europace 2014;16:1482-9.
4. Krahn AD, Longtin Y, Philippon F, et al. Prevention of arrhythmia device infection trial: The PADIT Trial. J Am Coll Cardiol 2018;72:3098-109.
5. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace 2015;17:767-77.
6. Birnie DH, Wang J, Alings M, et al. Risk factors for infections involving cardiac implanted electronic devices. J Am Coll Cardiol 2019;74:2845-54.
7. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2021;42:3427-520.
8. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial envelope to prevent cardiac implantable device infection. N Engl J Med 2019;380:1895-905.
9. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019;321:188-99.
10. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med 2001;345:804-9.
11. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med 2009;122:778.e1-7.
12. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. Diagn Microbiol Infect Dis 2007;57(3 suppl):13s-8s.
13. Cook DJ, Barbara DW, Singh KE, Dearani JA. Penicillin skin testing in cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1931-5.
14. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA 2001;285:2498-505.
15. Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. Am J Hosp Pharm 1994;51:79-84.
16. Blumenthal KG, Shenoy ES, Hurwitz S, et al. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. J Allergy Clin Immunol Pract 2014;2:407-13.
17. Blumenthal KG, Shenoy ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015;115:294-300.e2.
18. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part ii: antibiotic choice. Ann Thorac Surg 2007;83:1569-76.
19. Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2020;41:2012-32.

20. Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. J Clin Pathol 2014;67:1088-92.

21. Bolon MK, Morlote M, Weber SG, et al. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. Clin Infect Dis 2004;38:1357-63.

22. Vardakas KZ, Mavros MN, Roussos N, Falagas ME. Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design. Mayo Clin Proc 2012;87:349-63.

23. Li JT, Markus PJ, Osmon DR, et al. Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. Mayo Clin Proc 2000;75:902-6.

24. Phillips E, Louie M, Knowles SR, Simor AE, Oh PI. Cost-effectiveness analysis of six strategies for cardiovascular surgery prophylaxis in patients labeled penicillin allergic. Am J Health Syst Pharm 2000;57:339-45.

25. Beltran RJ, Kako H, Chovanec T, et al. Penicillin allergy and surgical prophylaxis: cephalosporin cross-reactivity risk in a pediatric tertiary care center. J Pediatr Surg 2015;50:856-9.

26. Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. JAMA Surg 2021;156:e210021.

27. Brockow K, Przybilla B, Aberer W, et al. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergology and Immunology (ÖGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). Allergo J Int 2015;24:94-105.