

Original Article

Direct Challenges to Penicillin-Based Antibiotics in the Inpatient Setting

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What is already known about this topic? Direct challenge to penicillin has been shown in multiple studies to be a safe and effective delabeling strategy in penicillin-allergic patients with low-risk reaction histories.

What does this article add to our knowledge? This article is among the first to demonstrate the safety and feasibility of direct challenge for adult inpatients reporting a low-risk penicillin allergy history.

How does this study impact current management guidelines? This study expands the inpatient setting data on the safety of direct challenge in adult inpatients with a low-risk reaction history, allowing for more patients to be delabeled without more costly and resource-intensive penicillin skin testing.

BACKGROUND: Direct challenge (DC) is an emerging safe and effective alternative to penicillin skin testing (PST) in patients reporting a low-risk reaction history, but limited data exist for the inpatient setting.

OBJECTIVE: To demonstrate the safety and efficacy of DC of penicillin-based antibiotics in the inpatient setting in patients with low-risk, cutaneous-only reaction histories more than 20 years ago.

METHODS: Adult inpatients reporting penicillin allergy and receiving antibiotics were screened by an infectious disease PharmD for appropriateness for penicillin allergy delabeling. Patients with low-risk, cutaneous-only reaction histories (rash, hives, itching) more than 20 years ago were offered a 3-step DC. Patients with a cutaneous reaction history less than 20 years ago, a history of angioedema, or reactions involving multiple body systems underwent PST followed by a 1-time observed dose of amoxicillin.

RESULTS: A total of 372 patients were screened during the study period, with 100 of these patients undergoing further

evaluation, 52 with histories appropriate for PST and 48 with histories appropriate for DC. In the PST group, 44 of 52 (84.6%) patients were PST negative. In the DC group, 47 of 48 (97.9%) patients initially tolerated the DC, with 2 of 48 (4.2%) experiencing a delayed reaction. The sole patient with an immediate DC reaction was treated with an antihistamine alone. Beta-lactam antibiotics were subsequently used in 56 of the 100 total patients. Total direct antibiotic savings was \$23,375.27. DC was less costly than PST, at \$206.18/patient versus \$419.63/patient.

CONCLUSIONS: DC is a safe, effective, and less expensive method for penicillin delabeling in adult inpatients with a low-risk, cutaneous-only reaction history more than 20 years ago. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Penicillin allergy; Penicillin allergy screening algorithm; Penicillin skin testing; Stewardship; Drug allergy; Delabeling; Direct challenge; Graded challenges

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INTRODUCTION

The penicillin (PCN) allergy label has received considerable attention in recent years.¹ It is the most commonly reported drug allergy, with 10% of outpatients² and upwards of 15% of inpatients³⁻⁵ reporting a history of PCN allergy. The individual harms of the PCN allergy label have been well established, including an increased length and cost of hospital stay, decreased infection cure rates, increased risk of infection recurrence, and increased risk of adverse events from use of second-line antibiotics.⁶⁻⁹ Blumenthal et al¹⁰ also recently demonstrated an increased mortality in patients with reported PCN allergy. From a public health standpoint, PCN allergy has been associated with higher health care costs and increased antimicrobial resistance, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and *Clostridioides difficile*.⁶⁻⁹ For these reasons, PCN allergy delabeling is recommended by multiple

*Abbreviations used**DC- Direct challenge**ID- Infectious disease**PAHA- Penicillin allergy history algorithm**PCN- Penicillin**PST- Penicillin skin testing**RGH- Rochester General Hospital*

organizations, including the American Academy of Allergy, Asthma, and Immunology,¹¹ the Infectious Disease Society of America,¹² and the Centers for Disease Control and Prevention.¹³

There is a growing body of literature evaluating PCN allergy delabeling in various targeted populations, different health care settings, and with different diagnostic approaches.^{1,14-23} Although PCN allergy delabeling was historically performed through penicillin skin testing (PST) followed by an oral challenge, there is accumulating data regarding the safety of direct oral challenges (DCs) in low-risk reaction histories. Most of these data are in the outpatient setting, and there are significantly less data regarding DC in the inpatient setting.²⁴⁻³⁰

We therefore evaluated the safety and feasibility of performing DC in low-risk adult patients in the inpatient setting, without transfer to a higher level of care, through modification of previously published PCN allergy history algorithms (PAHAs).^{20,30} We continued to perform PST followed by a single dose of amoxicillin in patients with higher risk reaction histories.

METHODS

Setting and data collection

This was a single-center, prospective study conducted at Rochester General Hospital, a 528-bed tertiary care medical center, from February 2018 through May 2019. At Rochester General Hospital, approximately 15% to 20% of inpatients report a PCN allergy (internal data). The study was approved by the institutional review board.

Inpatients 18 years or older receiving any antibiotic were identified via a pharmacy report, generated by the electronic health record (Hyperspace, Epic Systems Corporation, Verona, Wis). The report was screened daily by an infectious diseases (ID) PharmD (M.L.S.) for patients reporting a PCN allergy. Reported allergy history from the allergy field in the electronic health record was screened using the PAHA (Figure 1), which defined the management approach depending on the PCN allergy history. For patients identified as appropriate for further evaluation, the primary teams were contacted and/or an antimicrobial antibiotic stewardship progress note recommending an allergy evaluation was placed in the patient chart (Figure 2). Patients with a PCN allergy history of a severe cutaneous reaction, receiving empiric or targeted therapy for a resistant bacterial organism, or with an antibiotic regimen recommended by ID were not approached after PAHA screening. Additional exclusion criteria included inability to provide informed consent and pregnancy.

After screening by the ID PharmD and approval from the primary team, patients were asked to provide consent by either an allergy physician assistant or board-certified allergist. Patients providing consent and seen by the physician assistant were interviewed for their historical reaction via telemedicine as previously described,³¹ with the allergist conferencing in from the outpatient setting. Patients

providing consent to the allergist were evaluated in person. As defined by the PAHA, patients with a history of a cutaneous-only reaction including nonspecific rash, itching, or urticaria or an unknown reaction history more than 20 years ago were offered a 3-step DC to amoxicillin. Patients with nonspecific rash less than 20 years ago or any reaction suggestive of angioedema and/or extracutaneous IgE-mediated symptoms underwent usual PST, followed by a dose of amoxicillin or the PCN antibiotic indicated for their care. Patients were assigned to management on the basis of PAHA and therefore not randomized.

The 3-step DC approach was communicated to the primary team. The pharmacy protocol was built as a panel in the electronic health record. Patients received amoxicillin 8.75 mg (1/100th of the full dose), 87.5 mg (1/10th of the full dose), and 500 mg or 875 mg (full dose) separated by 30 minutes each or the penicillin-based antibiotic indicated for their care at 1/100th, 1/10th, and the full dose, also separated by 30 minutes. The amoxicillin dosing was chosen so amoxicillin/clavulanate could be ordered in the same panel. The DC was completed in the patients' current care setting, and level of care transfer (eg, to an intensive care unit) was not required.

For patients identified for PST, the major determinant of penicillin, penicilloyl polylysine (Pre-Pen, ALK, Round Rock, Texas), and PCN G 10,000 U/mL, histamine 6 mg/mL, and a saline negative control were used. Prick testing was carried out with Quintip skin testing devices (Hollister-Stier, Spokane, Wash) on the volar forearm.² A positive test result was defined as a wheal 3 mm or more than that achieved with the negative control in the setting of a reactive positive control. If skin prick test result was negative, intradermal testing was performed with the same materials except the histamine control was 0.02 mg/mL. Intradermal major determinant and PCN G were done in duplicate, with a positive test result again defined as 3 mm greater than that achieved with the negative control. A histamine control was placed on patients taking medications with antihistaminic properties, and testing was carried out if this control produced a wheal of 5 mm or greater. Patients with negative PST result were given a 1-time dose of amoxicillin 500 mg during their hospital stay or transitioned to a penicillin-based antibiotic indicated for their care. All patients received a 2-week follow-up phone call to assess the tolerability of their β -lactam antibiotic.

Cost analysis

To estimate the impact of both types of PCN evaluations on direct antibiotic expenditures, we subtracted the average wholesale price³² per day of antibiotic therapy after allergy evaluation from the average wholesale price per day of antibiotic therapy preevaluation. This value was then multiplied by the total duration of antibiotic therapy in days administered postevaluation. The impact on indirect costs such as pharmacist monitoring time, nursing administration and serum antibiotic concentration monitoring, and laboratory costs to analyze concentrations was not evaluated. For patients who underwent PST, the cost of penicilloyl polylysine, PCN G, and skin testing supplies (\$128.05) was subtracted from the amount billed for the allergy/immunology inpatient consult time (\$221.18) plus procedure time (\$326.50), totaling a net value of \$419.63/patient. Cost for the PST procedure was determined per the Revenue Integrity fee schedule, which is the Rochester Regional Health fee schedule of usual and customary prices billed for the specific type of testing. For patients who underwent graded challenge, the cost of amoxicillin plus pharmacist preparation time

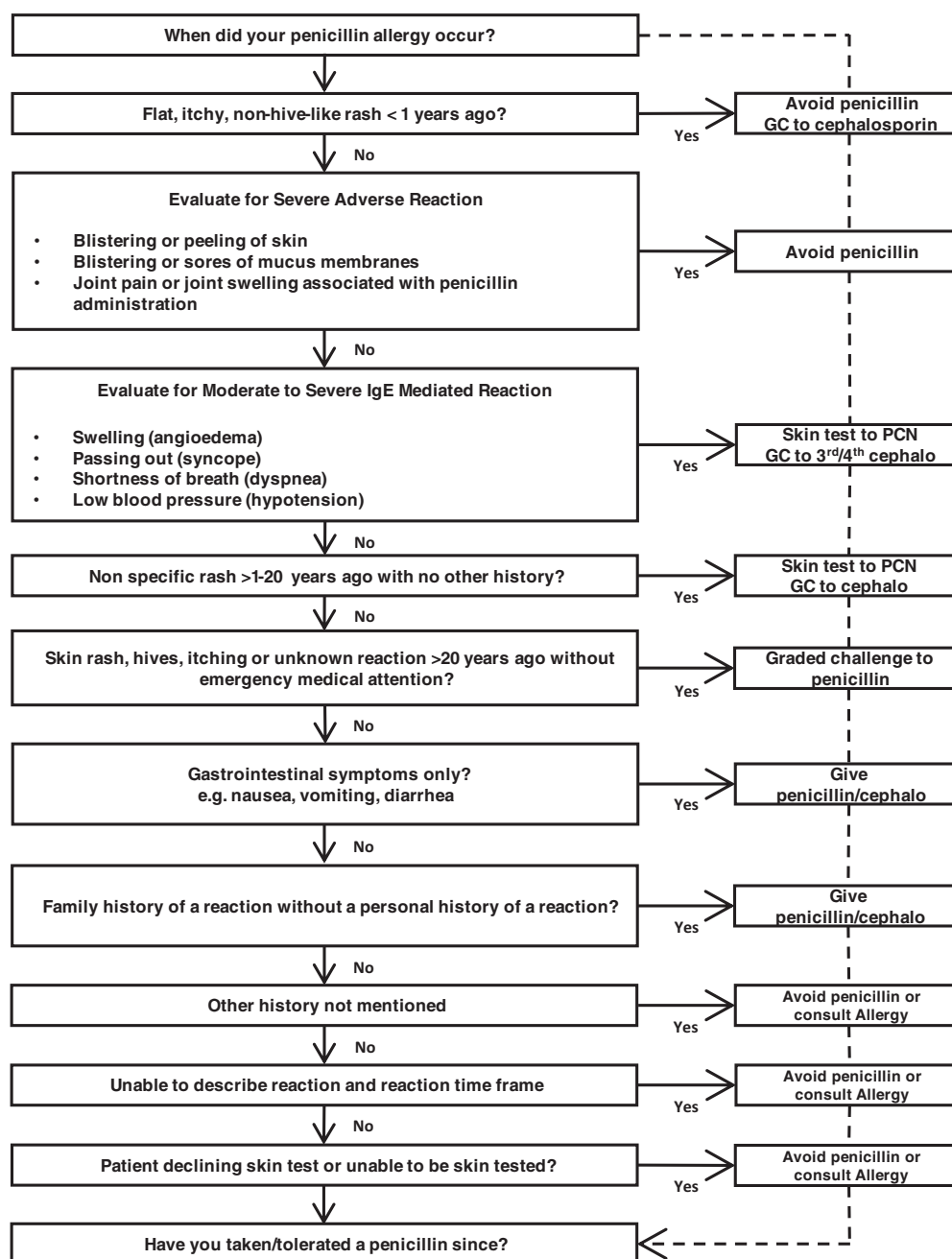


FIGURE 1. PCN allergy history algorithm. GC, Graded challenge.

(\$15) was subtracted from the amount billed for the allergy/immunology consult, totaling a net value of \$206.18/patient. Of note, as part of our research protocol, subjects were not billed for physician consultative time, but this figure was included in the cost analysis, as described above.

Data collection

Data collected included patient age, sex, race, hospital service, historical reaction to penicillin, type of infection, PAHA result, DC or PST result, antibiotic therapy before and after the PCN allergy evaluation, and tolerability of the β -lactam antibiotic as reported during the 2-week follow-up call.

Outcome measures and data analysis

The primary objective was to demonstrate the safety and feasibility of DC in the inpatient setting in patients with a low-risk PCN allergy history. Secondary outcomes included pre- and postevaluation antibiotic use, days of antibiotic therapy avoided, direct antibiotic cost savings after the PCN allergy evaluation, and cost of PST compared with DC. Descriptive statistics were used to detail outcomes.

RESULTS

A total of 372 patients were screened during the study period. Of these, 168 were not candidates to undergo further evaluation

Antimicrobial Stewardship Program (ASP) Recommendations

The ASP team would like to make the following suggestions for your patient's antimicrobial therapy:

Please consider placing an order for an Allergy consult

Microbiologic data and other considerations such as site of infection, antimicrobial efficacy, drug costs and dosing characteristics have been factored into our suggestions. We have not seen the patient; therefore, our suggestions should be considered in conjunction with all other patient factors. Our review is not intended to provide a clinical diagnosis and treatment plan, but to provide assistance in optimizing antimicrobial therapy once the primary clinical team has made a diagnosis and initiated therapy.

Based on a review of the above data, it was noted that your patient is receiving * with the indication of ***. Microbiologic workup ***. Upon chart review, it was noted that the patient has a documented penicillin allergy. Based on this information, the ASP team would like to make the following suggestions for your patient's antimicrobial therapy.**

Approximately 80% of patients with an IgE-mediated reaction to penicillin (i.e. anaphylaxis, angioedema, hives, itching) lose their sensitivity within 10 years. The use of penicillin skin testing to de-label patients that are no longer allergic has been shown to reduce healthcare exposure (LOS and readmission rates) and use of second-line antibiotic therapy.

Therefore, please consider calling Allergy (922-8350) for a penicillin allergy evaluation.

FIGURE 2. Example of Antimicrobial Stewardship Program note left in charts of patients in whom PCN allergy evaluation was recommended. LOS, Length of stay.

for various reasons (Figure 3). Of the 204 patients eligible for further evaluation, 50 had a primary team that independently requested an allergy evaluation and 154 had a verbal or written recommendation by the antimicrobial stewardship team. Of the 154 recommended to have an allergy evaluation consult, 120 (77.9%) patients were evaluated by the allergy service, whereas there was no request for allergy evaluation for 34 (22.1%) patients. A total of 100 patients consented to undergo PST or DC depending on their history.

In these 100 patients, 52 underwent PST and 48 underwent a DC to a penicillin-based antibiotic (Table I). The average age of the PST and DC groups was 56.5 ± 16.3 and 65.2 ± 16.1 years, respectively (Table I). There were 29 (55.8%) females in the PST group and 34 (70.8%) females in the DC group. The most commonly reported reactions in the PST group were hives and angioedema (23.1%), anaphylaxis (19.2%), and angioedema alone (13.5%). The only reactions in the DC group were rash (45.8%), hives (41.7%), and itching (4.2%) (Table I). For both groups, the most common primary team was the internal medicine service in 70 of 100 patients, followed by general surgery (15 of 100), surgical subspecialties (6 of 100), observation (4 of 100), orthopedics (2 of 100), obstetrics/gynecology (2 of 100), and pediatrics (1 of 100, patient >18 years old).

In the PST group, 44 (84.6%) patients had a negative test result, 6 (11.5%) patients had a positive test result, and 2 (3.8%)

patients had a blocked histamine (and were subsequently given information regarding outpatient evaluation of their PCN allergy). All 44 patients with a negative test result tolerated a dose of amoxicillin (Table II). Of the patients with a positive PST result, all were positive to PCN G at the intradermal level with a wheal greater than 5 mm (Table III). In the DC group, 47 (97.9%) patients tolerated the DC without an immediate reaction and 1 (2.1%) had a reaction consisting of mild swelling and redness under the eyes 30 minutes after the second step of the challenge, which was successfully treated with oral diphenhydramine with resolution of symptoms within an hour (Table II). There were no patients who required treatment with epinephrine in either group. For the patients with a positive PST result or immediate DC, the low risk of cross-reactivity was discussed, and if medically indicated, the use of cephalosporins was recommended via a 1- or 2-step DC. At the 2-week follow-up call, 2 patients in the DC group reported delayed reactions: 1 patient reported a rash with amoxicillin/clavulanate on day 17 of therapy (10 days after discharge) and 1 patient reported facial swelling and nausea/vomiting with amoxicillin/clavulanate on the day after the challenge. One patient from the PST group experienced a rash with cefazolin on day 17 of cefazolin therapy, as they were transitioned to a cephalosporin per the primary team after a negative PST result. A total of 53 patients confirmed verbally at the follow-up call that they tolerated a PCN-based antibiotic,

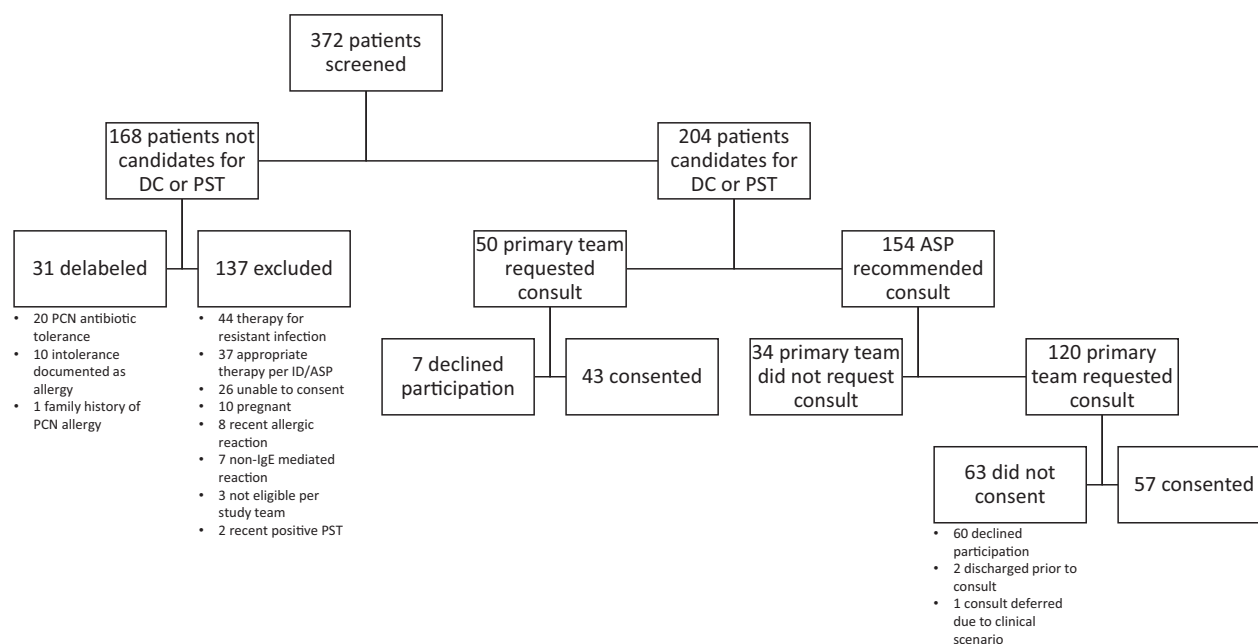


FIGURE 3. Details regarding all patients screened. *ASP*, Antimicrobial Stewardship Program.

TABLE I. Patient demographics

Patient characteristics	PST	DC
Patients, n	52	48
Age (y), mean $\pm$ SD	56.5 $\pm$ 16.3	65.2 $\pm$ 16.1
Sex: female, n (%)	29 (55.8)	34 (70.8)
White, n (%)	42 (80.8)	37 (77.1)
Black, n (%)	5 (9.6)	9 (18.8)
Hispanic, n (%)	5 (9.6)	2 (4.2)
Reaction history, n (%)	PST	DC
Hives and angioedema	12 (23.1)	0
Anaphylaxis	10 (19.2)	0
Angioedema	7 (13.5)	0
Rash	6 (11.5)	22 (45.8)
Hives	5 (9.6)	20 (41.7)
Unknown	5 (9.6)	4 (8.3)
Dyspnea	4 (7.7)	0
Itching	2 (3.8)	2 (4.2)
History of +PST	1 (1.9)	0

whereas 14 patients had a message left to call if they experienced problems and none called back. Twenty-one patients were lost to follow-up.

For both the PST and DC groups (100 patients), there were 56 patients who were transitioned to a penicillin-based antibiotic, 10 to a first- or second-generation cephalosporin and 4 to a third-generation cephalosporin. There were 13 patients who were transitioned to a non-beta-lactam antibiotic. Some patients received a combination of these classes. There were 28 patients in whom therapy was not impacted. Pre- and postevaluation antibiotic usage is illustrated in [Figure 4](#).

There were a total of 783 days of second-line antibiotic therapy avoided on the basis of antibiotic indication and recommended length of therapy ([Table IV](#)). Second-line antibiotic

TABLE II. PCN allergy evaluation results

	PST (followed by challenge)	DC (without skin testing)
Patients, n	52	48
Positive PST result, n (%)	6 (11.5)	NA
Negative PST result, n (%)	44 (84.6)	NA
Blocked histamine/TND, n (%)	2 (3.8)	NA
DC Fail immediate, n (%)	NA	1 (2.1)
DC Fail delayed, n (%)	NA	2 (4.2)
DC Pass, n (%)	NA	45 (93.8)

NA, Not applicable/available; TND, testing not done.

days of therapy avoided included 273 days of vancomycin, 100 days of clindamycin, 62 days of fluorquinolones, 61 days of aztreonam, and 23 days of linezolid. The cost of PST for the 52 patients tested was \$21,820.76, and for the 48 graded challenge patients, the cost of the evaluation was \$9896.64. The total cost of evaluation for both groups was \$31,717.40. Direct antibiotic cost avoidance was calculated to be \$14,724.85 in the 29 PST patients who were transitioned from second-line antibiotics and \$8650.42 in the 43 graded challenge patients in whom antibiotic therapy was changed, for total cost avoidance of \$23,375.27.

DISCUSSION

Our study adds to the growing body of evidence for DC in patients with a low-risk PCN allergy history, and is among the first to demonstrate the feasibility and preliminary safety of this approach in the inpatient setting for adult patients. Of course, the DC approach carries the same benefits of delabeling as PST, and we demonstrate direct cost savings, avoidance of second-line antibiotics, and an increased use of beta-lactam antibiotics regardless of the approach used.

TABLE III. Positive PST result patient information

Patients with positive PST result					
Patient no. (age, sex)	Historical reaction	Time elapsed (y)	Index drug	Positive PST result*	Size of PST (wheal × flare)
1 (46, F)	Rash	10	Amoxicillin	PCN G	5 × 15, 5 × 15
2 (39, M)*	Unknown	39	PCN	PCN G	5 × 15, 5 × 15
3 (93, F)	Rash, angioedema, dyspnea	70	PCN	PCN G	5 × 10, 5 × 10
4 (76, M)	Urticaria, angioedema	40	PCN	PCN G	5 × 5, 5 × 5
5 (35, F)	Urticaria	19	Amoxicillin	PCN G	5 × 25, 5 × 25
6 (51, M)	Unknown	“Childhood”	PCN	PCN G	5 × 10, 5 × 10

*All PST positives were at intradermal level.

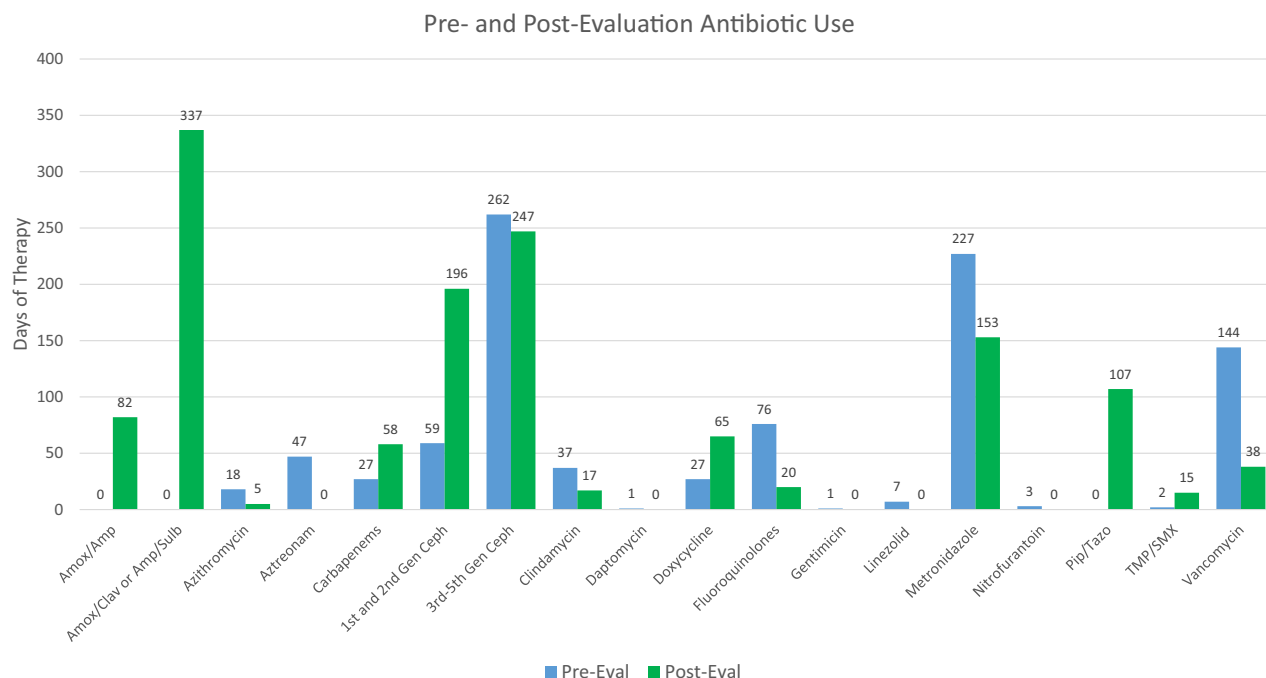


FIGURE 4. Antibiotic use before and after PCN allergy evaluations. *Amox*, Amoxicillin; *Amox/Clav*, amoxicillin/clavulanate; *Amp*, ampicillin; *Amp/Sulb*, ampicillin/sulbactam; *Ceph*, cephalosporin; *Eval*, evaluation; *Pip/Tazo*, piperacillin/tazobactam; *TMP/SMX*, trimethoprim/sulfamethoxazole.

Most literature regarding DC is from the outpatient setting, where multiple groups have demonstrated the safety of this approach for low-risk adult and pediatric patients.²⁴⁻³⁰ Iammatteo et al²⁸ reported on 155 outpatients who received placebo and a 2-step challenge to amoxicillin. The authors demonstrated immune-mediated reactions in 4 of 155 (2.6%) patients, whereas 31 patients experienced “nonallergic reactions.” Our reaction rate to DC was similar (1 of 48 patients [2.1%]), but interestingly, we did not have patients experiencing nonallergic symptoms. We previously demonstrated a similar rate of reactions to DC in the outpatient setting (3 of 79 patients [3.8%]),³⁰ and in both settings, reactions were mild and treated only with an antihistamine. Trubiano et al²⁵ reported DC in 23 cancer and 23 noncancer patients, where 29 of 46 (63%) of these patients were challenged in the inpatient setting, and all tolerated the challenge.

As shown in previous studies,^{19,20} there was a decrease in second-line antibiotic use, and an increase in beta-lactam use in our study cohort after PCN allergy evaluation, regardless of whether it was completed though PST or DC. A total of 56 of 100 patients

transitioned to a penicillin-based antibiotic, and 14 patients transitioned to a cephalosporin. The benefits of these antibiotics over others, such as vancomycin, fluoroquinolones, and/or aztreonam, among others, have been previously discussed.^{6,7,33} We demonstrated similar changes in antibiotic therapy with DC as compared with PST, raising the possibility of eliminating the sometimes cumbersome and/or scarcely available step of PST with similar beneficial outcomes. The lack of allergy/immunology availability has been discussed as a barrier to PCN allergy delabeling,³⁴ and our approach could allow for an allergist to “oversee” multiple programs without having to be physically present, similar to what has been shown with cephalosporins in the Partners Health Care system³⁵ in which hospitals without allergy consultation challenged cephalosporins in patients with PCN allergy. Furthermore, our approach is an option for other specialties invested in PCN allergy delabeling (ID, pharmacy, hospital medicine) to evaluate low-risk patients without direct allergy/immunology input.

In our study, patients received DC in their current level of care, and were not transferred to higher levels of care, such as the

TABLE IV. Days of antibiotic therapy avoided postevaluation

Antibiotic	Days avoided
Aztreonam	71
Carbapenems	37
Cephalosporins	195
Clindamycin	100
Doxycycline	19
Fluoroquinolones	62
Linezolid	23
Vancomycin	273
Other	3
Total days saved	783

medical intensive care unit, for monitoring. This is encouraging preliminary information, and should be reassuring to other members of the health care team with less expertise in PCN allergy delabeling. It is notable that 34 of 154 (22%) patients for whom the Antimicrobial Stewardship Program team recommended an allergy consult did not have their primary team request one, but reasons for this finding were not elicited. Further data regarding the safety of DC may help to further convince health care professionals regarding the safety of this approach.

Another emerging advantage of DC in low-risk patients with PCN allergy that we have discussed previously³⁰ is that PST carries with it the risk of false-positive testing. We had higher numbers of PST positives compared with DC in our current cohort. This finding could potentially be explained by our inclusion of patients with higher risk reaction histories in patients undergoing PST. However, if our inpatient results are similar to our outpatient results³⁰ and those of others,^{24,28} then proceeding with DC in low-risk patients has the potential to delabel more patients by removing this risk of false-positive testing based on sensitization alone. Furthermore, DC was less costly than PST in our analysis, which we have previously shown in the outpatient setting.³⁰ One consideration against DC is that some patients may prefer to visualize the negative PST result for reassurance before taking a penicillin-based antibiotic, and we certainly acknowledge this utility of PST.

There were significant numbers of patients screened in our study who ultimately did not undergo evaluation, and this is a limitation of such a study in the inpatient setting. We chose not to target patients with resistant infections, and these patients were therefore not evaluated and continued on appropriate antibiotics for resistant organisms. Similar to the study by Teremi et al,³⁵ we had a significant number of screened patients who did not wish to undergo evaluation because they were overwhelmed with their admission, did not feel up to it, or did not wish to risk an adverse event, however small this risk was. This highlights not only the importance of continued education regarding the consequences of the PCN allergy label but also the value of proactively evaluating the PCN allergy label when patients are in good health and in the outpatient setting, as has been advocated by national societies.¹¹

Our study has limitations, the most important of which is the small sample size of patients undergoing DC. With the overall low-risk of anaphylaxis to PCN, significantly larger numbers are needed to prove safety, as has been recently discussed.³⁶ However, our preliminary data are reassuring for both patients and

health care providers. We acknowledge that our 20-year period to define low risk is overly conservative; since the completion of this study, this has been modified to 10 years. We recognize that our study could have been completed with a 2-step, rather than a 3-step challenge. Our hospital pharmacy was accustomed to 3-step challenges, so we did not elect to pursue this change for the purposes of this study. We have also not tracked outcome data beyond antibiotic change during the same admission as evaluation, and longer follow-up data regarding future antibiotic use and admissions would be informative and would likely reflect additional cost savings. Although we completed a 2-week follow-up phone call and asked patients to contact the study staff for adverse reactions, this follow-up is not long enough to capture some delayed reactions or problems with subsequent PCN antibiotic courses. We did not track the rate of PCN-allergy relabeling, which also has been demonstrated to be a problem in programs such as ours.^{37,38} We acknowledge that the cost of PCN allergy evaluations is not immediately covered by direct antibiotic cost savings in our analysis. However, future cost savings not accounted for in this study are to be expected, such as future antibiotic cost savings and/or decreased adverse events from second-line antibiotics. Given the safety demonstrated with a DC in low-risk patients, future cost savings can also be expected through increased use of this less expensive evaluation, which could potentially also occur without a formal allergy/immunology consult. Finally, we offer that using a physician assistant and telemedicine is not necessary in all cases, and that approaches may be tailored outside of the study setting without compromising patient safety.

CONCLUSIONS

We are among the first studies to demonstrate the feasibility and safety of DC in inpatients with a low-risk PCN allergy reaction history. This approach can be incorporated into PCN allergy delabeling programs to maximize institutional ability to take advantage of this important individual and public health service.

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