

Risk of Allergic Reactions to Recurrent Intravenous Penicillin Administration in Penicillin Skin Test Negative Patients



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What is already known about this topic? Patients with histories of penicillin allergy but with negative skin test results may be at increased risk for penicillin resensitization following intravenous penicillins.

What does this article add to our knowledge? The risk of having an immediate reaction to intravenous penicillin appears very low in penicillin skin test negative patients who have received repeated courses of intravenous penicillin therapy.

How does this study impact current management guidelines? Repeat penicillin skin testing after a well-tolerated course of intravenous penicillin therapy appears unnecessary.

BACKGROUND: Patients with a history of penicillin allergy who are found to be skin test negative to penicillin are able to tolerate repeated oral doses of penicillin with low rates of resensitization. However, the resensitization rate after repeated doses of intravenous penicillin is less clear.

OBJECTIVE: We sought to evaluate the risk of allergic reactions to repeated doses of intravenous penicillin in patients who previously reported penicillin allergy and were found to be penicillin skin test and oral challenge negative.

METHODS: A retrospective review was conducted between 2010 and 2016 of adult patients who were treated at our academically affiliated hospitals. Patients included in the review had negative penicillin allergy testing and were treated with 2 or more courses of intravenous penicillins. Charts were evaluated to identify any adverse drug reactions.

RESULTS: Thirty-two patients met our inclusion criteria. The index penicillin-associated reactions ranged from rash to hypotension and were, for the most part, remote as 75% had reported reactions more than 10 years previously. More than 50% of patients received 3 or more courses of intravenous penicillins. The most frequently repeated intravenous penicillin overall was piperacillin/tazobactam. Thirty-two patients received a total of

111 courses of intravenous penicillins and none developed an immediate hypersensitivity reaction.

CONCLUSIONS: In patients who report penicillin allergy and have negative penicillin allergy testing, repeated administration of intravenous penicillin antibiotics appears to be safe. Larger prospective studies should be performed to confirm these observations. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:196-200)

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Clinicians commonly encounter patients with a history of allergy to antibiotics and among these, penicillin allergy is the most often reported.¹ Approximately 10% of hospitalized patients in the United States report a history of penicillin allergy.^{1,2} Recent US studies indicate that approximately 98% of patients reporting penicillin allergy are not truly allergic and could safely receive penicillin.^{3,4} In addition, penicillin allergy wanes with time, with approximately 50% of allergic cases at 5 years and roughly 80% at 10 years showing tolerance.^{5,6} Despite these trends, penicillin antibiotics continue to be a major cause of anaphylaxis. A recent US study on fatal anaphylaxis found antibiotics to be the most common identifiable cause, with penicillins being the most common culprit antibiotic.⁷ Administration of intravenous penicillin (compared with other methods of administration) is considered to have the highest risk of provoking anaphylaxis in individuals sensitized to penicillin.⁸

Current evaluation for patients reporting penicillin skin testing includes a history and penicillin skin testing, and when negative, a confirmatory oral challenge, often with amoxicillin, is typically performed.³ Previous studies have shown that patients who have been evaluated and have negative penicillin skin test results are able to tolerate repeat oral doses of penicillin with low rates of resensitization (ie, redevelopment of a penicillin allergy).⁹⁻¹¹ What has not been conclusively evaluated is the risk of resensitization after repeated doses of intravenous penicillin.

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Abbreviations used
EMR- electronic medical record

Few studies have been performed to determine the risk of resensitization after parenteral courses of penicillin with mixed results. Parker et al¹² described 18 adults who reported penicillin allergy and had negative penicillin skin test results, followed by administration of intravenous penicillins or cephalosporins.¹² Of the 18 total subjects treated, 3 patients (16%) developed evidence of resensitization based on development of a positive penicillin skin test result. Lopez-Serrano et al¹³ evaluated 207 patients with penicillin allergy who had initially negative skin test results and negative challenges with both oral amoxicillin and intramuscular benzylpenicillin.¹³ Ten to 30 days after their initial evaluation, they performed repeat penicillin skin tests and challenges (if negative). Eleven patients (5%) had either converted to a positive penicillin skin test ($n = 6$) or reacted to challenge ($n = 5$) with benzylpenicillin or amoxicillin. Bittner and Greenberger¹⁴ described 30 subjects who reported penicillin allergy and had negative penicillin skin testing who received at least 1 course of a parenteral cephalosporin or β -lactam antibiotic. None of the identified patients had evidence of an IgE-mediated reaction with readministration of antibiotics. Based on this information, the Drug Allergy Practice Parameters states that “resensitization after high-dose parenteral treatment with penicillin appears to be more likely; therefore, repeat penicillin skin testing in this situation may be warranted.”¹⁵

In light of this conflicting data, we sought to evaluate the risk of allergic reactions after repeated courses of intravenous penicillins in subjects who report a history of penicillin allergy and have subsequent negative skin testing and challenge to a penicillin.

METHODS

Subjects

Records were reviewed retrospectively from adult patients treated at the University of Texas Southwestern Medical Center hospitals and clinics or the Parkland Health and Hospital System from September 1, 2010, to April 1, 2016. A list of subjects who underwent penicillin skin testing (either as an inpatient or as an outpatient) was obtained by way of electronic medical record (EMR) query of the University of Texas Southwestern Medical Center hospitals and clinics. At Parkland Hospital, a program of inpatient penicillin skin testing has been established since November 2014, and a list was obtained of patients who were identified as having been tested via this program.⁴ Patients were included in this retrospective study if they met the following criteria: (1) had evidence of a previous negative penicillin skin test and amoxicillin challenge and (2) after negative penicillin testing received at least 2 subsequent courses of a parenteral penicillin documented in the EMR.

Antibiotic courses and exposures

A “course” of intravenous penicillin could be as little as a single dose (such as perioperative dosing) or as long as needed to treat the underlying problem while hospitalized. A continuous antibiotic course was defined as intravenous penicillin administration with a break in dosing of no longer than 7 days. This definition allowed for subject differences with respect to dosing because dosing may differ among subjects with different comorbid conditions. It would

include breaks between hospitalizations and/or treatments for specific disease process (eg, a neutropenic patient finishing piperacillin/tazobactam for hospital-associated pneumonia and then, 4 days later, receiving piperacillin/tazobactam again for fever of unknown origin). Multiple penicillin types could be given during this time yet the period would still be defined as a continuous course. An “antibiotic exposure” was defined as having received a specific antibiotic. Patients may be exposed to more than 1 antibiotic during a single course (eg, to narrow treatment from piperacillin/tazobactam to ampicillin). After each course of penicillin, the EMR was reviewed for evidence of immediate allergic reactions as well as delayed adverse drug reactions.

Penicillin skin testing and amoxicillin challenge

A uniform testing protocol was used at both institutions. Penicillin skin testing was performed with PrePen (benzyl-penicilloypolylysine; AllerQuest LLC, ALK-Abello, Inc., Hørsholm, Denmark) and Penicillin G (potassium penicillin G; Sandoz, Inc, Princeton, NJ; diluted to 10,000 units/mL). If percutaneous test results are negative at 15 minutes, intradermal testing in duplicate is performed. A wheal of 3 mm or greater accompanied by flare on percutaneous testing is considered positive. A change in intradermal wheal (typically an initial wheal is 3–5 mm) of greater than 3 mm in any direction accompanied by a flare is considered positive. If skin testing is negative, an oral challenge with 500 mg of amoxicillin and 1-hour observation was performed. If patients were being evaluated in the hospitalized setting where intravenous penicillin is needed acutely, a dose of intravenous penicillin may be given in lieu of the amoxicillin challenge.

The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center (STU 122013-054).

RESULTS

Subjects

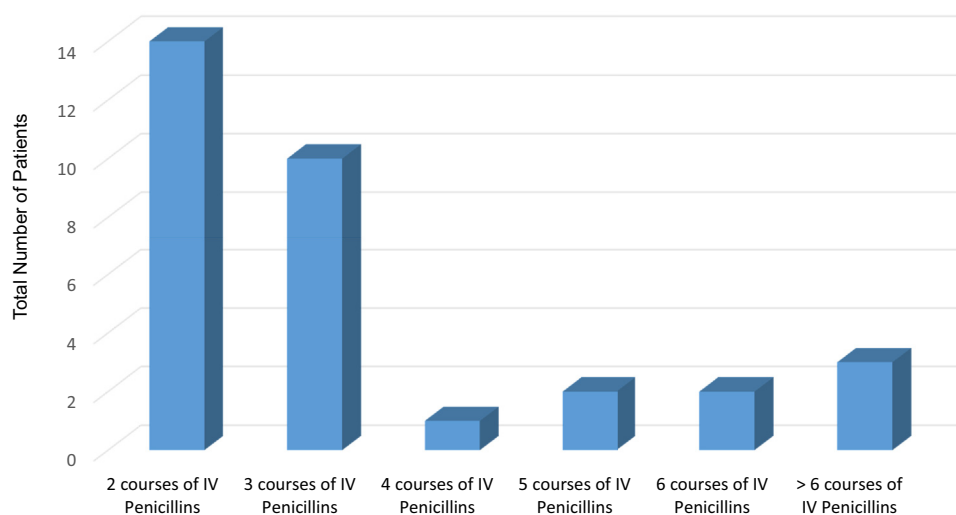
Thirty-two subjects met our inclusion criteria (Table I). Of these, 4 underwent penicillin skin testing in an ambulatory setting and 28 were tested while hospitalized. Seventeen (53%) of the 32 subjects were women. The average age at penicillin skin testing was 46.9 years (range, 24–79 years). In regard to race, 13 were documented in the EMR to be black, 10 white, 3 Hispanic, and 6 unknown. Most subjects (75%) had remote (>10 years ago) historical reactions to penicillin; however, 16% had reported allergic reactions to penicillin within a year of penicillin testing. Historical reactions to penicillins varied, with the majority having cutaneous reactions. One subject reported symptoms and signs consistent with anaphylactic shock. Surprisingly, only 1 subject could not recall the type of reaction to penicillin.

Intravenous penicillin courses

The total number of parenteral courses of penicillin antibiotics observed was 111. The mean number of antibiotic courses per patient was 3.5 courses (range, 2–12 courses) (Figure 1). More than 50% of patients received 3 or more courses of intravenous penicillins. Patients were exposed to 5 different intravenous penicillins: ticarcillin, nafcillin, ampicillin, penicillin G, and piperacillin. Piperacillin was the most prolific, with 30 of the 32 subjects being exposed. Penicillin G was the least prolific, with 1 subject being exposed once.

TABLE I. Patients' demographic characteristics

Demographic characteristics of patients who underwent penicillin skin testing	Value
Total number of patients	32
Sex: female, n (%)	17 (53)
Race, n (%)	
Black	13 (40)
White	10 (31)
Unknown	6 (19)
Hispanic	3 (9)
Mean age in years (range) at time of penicillin skin testing	46.9 (24-79)
Mean (range) in days from penicillin skin test to first course of penicillin	19 (<1-933)
Median (range) number in days from penicillin skin to second course of penicillin	129 (14-1055)
Penicillin skin testing done as inpatient, n (%)	28 (87.5)
Time interval from historical reaction to penicillin administration	No. of subjects (%)
<1 y	5 (16)
1-<5 y	2 (6)
5-<10 y	1 (3)
10-<20 y	5 (16)
>20 y	19 (59)
Reported previous reaction to penicillin	No. of subjects (%)
Respiratory complaint	3 (9)
Hives	11 (34)
Angioedema/swelling	6 (19)
Rash	19 (59)
Other	4 (13)
Hypotension	1 (3)
Gastrointestinal symptoms	2 (6)
Unknown	1 (3)

**FIGURE 1.** Number of intravenous (IV) courses of penicillins per patient. The 32 patients received a total of 111 courses of penicillins with a mean of 3.5 courses per patient.

The time between negative penicillin skin testing and the first parenteral course of penicillin was a median of 19 days (range, <1 day-933 days). With respect to time from

negative penicillin skin testing to the second course of an intravenous penicillin, the median was 129 days (range, 14-1055 days).

Adverse reactions to intravenous penicillin therapy after negative skin test results

Immediate reactions to intravenous penicillins. None of the 32 subjects who reported a history of penicillin allergy with subsequent negative penicillin skin testing and then were treated with repeated courses of intravenous penicillins had documentation of an immediate (ie, IgE-mediated) reaction.

Delayed reactions to intravenous penicillins

Three subjects reported delayed adverse reactions—1 subject with subjective throat and ocular pruritus, 1 subject with acute interstitial nephritis, and 1 subject with a benign exanthema.

The first subject with a reported delayed adverse reaction was a 57-year-old woman with a medical history of systemic lupus erythematosus who reported a history of facial swelling more than 20 years before her negative penicillin skin testing. She received 2 separate 5-day courses of piperacillin/tazobactam uneventfully. The time between courses was 67 days. Her third course of piperacillin/tazobactam was 24 days after finishing the second course and was a single dose given preoperatively for forearm tenosynovitis debridement. The following day, she complained of subjective throat and conjunctival pruritus. No objective findings were documented on the examination of the on-call physician and she was administered a single dose of diphenhydramine more than 10 hours after piperacillin/tazobactam administration for this complaint. At this time, penicillin allergy was placed back on her medication allergy list in the EMR.

The second subject with a reported delayed adverse reaction was a 36-year-old Hispanic female with a medical history notable for hypertension, diabetes mellitus type 2, morbid obesity, diastolic heart failure, and chronic kidney disease. She reported hives (on her arm and possibly her face) with “penicillin” orally 2 to 3 weeks before her negative penicillin testing. She received a 3-day course of piperacillin/tazobactam for cellulitis, starting 25 days after negative penicillin skin testing. On this admission she was also noted to have pulmonary edema on chest radiography and was started on loop diuretics. On day 3 of her piperacillin/tazobactam course, she reported nonpruritic erythema on her arms bilaterally, and on examination she was noted to have a flushed face and to have erythroderma on her chest and bilateral arms. Concurrently, she was noted to have an acute kidney injury. Piperacillin/tazobactam and loop diuretics were discontinued at this time. Both the rash and her acute kidney injury resolved completely in less than a week. Urine eosinophil level was measured to be zero. A nephrology consultant documented the subject’s acute kidney injury etiology to be uncertain but possibly related to prerenal acute tubular necrosis in the setting of diastolic heart failure with loop diuretic use, angiotensin-converting enzyme use, infection, and acute interstitial nephritis. Approximately 9 months later, she received a second course of intravenous piperacillin/tazobactam for 16 days without any documented adverse events. Five months later, she began her third course of piperacillin/tazobactam for 8 days for infection of a diabetic foot ulcer and suffered no adverse reaction.

The third subject with a reported delayed adverse reaction was a 30-year-old male with medical history notable for HIV/AIDS (CD4 count of <200 cells/ μ L) and syphilis. The subject reported a history of a skin rash and hives to penicillin that occurred more than 20 years before negative penicillin skin

testing. The day of the negative penicillin skin testing he received an intramuscular penicillin G dose for syphilis. His first course of an intravenous piperacillin/tazobactam was started 38 days later when he received a 3-day course for urosepsis. During this 3-day course of piperacillin/tazobactam, he also received benzathine penicillin intramuscularly for secondary syphilis, oral azithromycin for low CD4 count, and ciprofloxacin, moxifloxacin, and vancomycin for urosepsis. The day after discontinuation of piperacillin/tazobactam he developed a benign exanthema confirmed via dermatology consult. The patient’s therapy was changed to ceftriaxone intravenously for urosepsis. The rash was documented to resolve in less than 48 hours. No significant abnormalities in liver function enzymes or serum creatinine abnormalities occurred, and no exfoliative dermatitis ensued. The infectious disease consultants suggested that the patient continue intramuscular penicillins for treatment of syphilis, as the rash was noted to be mild. Approximately 2 months later, he received a second course of piperacillin/tazobactam for 1 day as a treatment for sepsis. No adverse reaction was noted. Five months later he received a third course of piperacillin/tazobactam for 1 day, given for fever, and no adverse event was noted.

DISCUSSION

In this study of 32 patients with a history of penicillin allergy who had negative penicillin allergy testing and received at least 2 subsequent intravenous penicillin therapies (total of 111 courses), none developed evidence of an immediate IgE-mediated type of reaction. The estimated reaction rate is 0% with a 95% CI of 0% to 3.3% to 11%. This wide range of the upper limit of the CI is based on how one determines the sample size. The upper limit of the CI is 3.3% if each penicillin treatment course is treated independently ($n = 111$) and is 11% if calculated with the 32 patients ($n = 32$).

We chose to use clinical tolerance of intravenous penicillin as our primary outcome rather than penicillin skin testing. The true reference standard for documenting the absence of penicillin allergy is the tolerance of the drug. The clinical significance of an isolated positive penicillin skin test result is unclear because studies have not defined the true positive predictive value. Some studies have shown that some patients with positive penicillin skin test results can tolerate penicillins.¹⁶ Although sensitization (ie, a positive skin test result) without clinical allergy is well recognized in other IgE-mediated reactions such as food allergy, this concept is not well accepted in drug allergy. However, it is quite likely that some patients who are not truly allergic may have positive penicillin skin test results. To our knowledge, this is the largest series examining clinical tolerance to repeated courses of intravenous penicillins in patients with a history of penicillin allergy but negative penicillin skin test results. More than 50% of the patients received 3 or more courses of intravenous penicillin after reporting penicillin allergy and demonstrating negative penicillin allergy testing.

Few other adverse events were documented in these patients. Two subjects were noted to have delayed rashes during their initial course of intravenous penicillin therapy but afterward, both patients tolerated 2 subsequent intravenous courses of penicillin without reaction. One of these subjects also had acute kidney injury (due to multiple etiologies including volume depletion) to their first course but did not have evidence of acute kidney injury with subsequent courses. Even if these cases were

due to a drug-induced exanthem or a drug-induced acute interstitial nephritis, it would not be detected via repeat penicillin skin testing. The subject who had subjective throat and ocular pruritus had no documentation of conjunctival injection or oropharyngeal abnormalities and no abnormal vital signs were noted. No epinephrine was given. The documentation of these delayed subjective symptoms was 10 hours after completion of the intravenous penicillin (her third course) and is not in keeping with an IgE-mediated reaction. This patient has not had further penicillin skin testing and challenge to confirm or refute tolerance to penicillins.

The results of our study are similar to the findings of Bittner and Greenberger who concluded that their data did not support penicillin skin testing before repeated courses of penicillins. In contrast to their study, all our patients received intravenous courses of penicillins initially and all received intravenous penicillins (not other beta-lactams) subsequently. This strengthens the findings of the present study as it applies purely to penicillin allergy with repeated intravenous courses and not implications related to cross-reactivity between beta-lactams. In contrast, Parker et al¹² found that 3 of 18 patients treated with intravenous beta-lactams developed positive penicillin skin test results. An important caveat of their data is the definition of resensitization via evidence of positive penicillin skin test results. Whether these patients were clinically allergic to penicillin is not known and it is possible that this could have been due to sensitization without clinical allergy. Last, our data differ from the data from Lopez-Serrano who evaluated patients after a single intramuscular dose of benzylpenicillin and found that 11 of 207 had evidence of resensitization. Six of these patients were determined to have resensitization based on positive skin test results and thus the issue of true clinical allergy as mentioned previously is unclear. However, 4 patients were clinically reactive to benzylpenicillin with negative penicillin skin test results. Thus, even if penicillin skin tests were repeated as suggested by the Drug Allergy Practice Parameters, these patients would have been missed. Furthermore, these patients all received benzylpenicillin intramuscularly, and perhaps the risk of resensitization is different with this long-acting penicillin via this route of administration.

There are several limitations to our study. Because of its retrospective nature, we were able to observe only those previous occurrences that were documented in the EMR. Furthermore, the patients observed were largely in an inpatient setting. Delayed findings, if they occurred, have the potential to be missed. Some subjects were discharged to long-term care facilities or nursing homes to continue intravenous penicillin treatment or received additional treatment via home health services. Observation of these courses was not evaluated with the same certainty as the course of a patient hospitalized at one of the institutions included in the analysis. Nevertheless, these delayed exanthema are not predicted by penicillin skin tests.

In conclusion, we found no immediate reactions in 32 subjects with a history of penicillin allergy who had negative penicillin skin testing and challenge and received a total of 111 courses of parenteral penicillins with a mean of 3.5 courses per patient. The findings in this series do not support the practice of repeated penicillin skin testing before repeat administration of intravenous penicillin in patients who have been previously found to have negative penicillin skin testing and tolerated a course of intravenous penicillin. Larger prospective studies should be performed to confirm these observations.

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