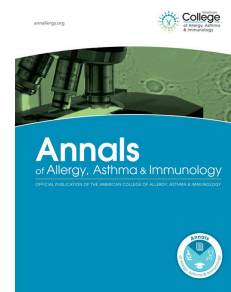


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Negative Penicillin Skin Testing Induced Anaphylaxis with Concurrent Beta Blocker and Angiotensin-converting Enzyme Inhibitor Use

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Phuong Daniels DPT, OMS-II, Maaz Jalil DO, Chelsea Michaud DO, and Robert Hostoffer DO: conception and design of the study, data generation, analysis and interpretation of the data, and preparation and clinical revision of the manuscript.

1 Penicillin allergy occurs at a prevalence rate of 0.7% to 10% in adults and children.¹
2 Hypersensitivity to penicillin is commonly evaluated with a protocol that consists of skin testing
3 with skin prick and intradermal tests, followed by an oral amoxicillin challenge if the former
4 tests are negative.^{2,3} Recent studies have shown that drug hypersensitivity may be directly
5 evaluated by an oral challenge without a preceding skin test in low-risk populations.^{4,5} We
6 present the first case of anaphylaxis following negative skin prick and intradermal tests with
7 penicillin and benzylpenicilloyl polylysine.

8 An 85-year-old female was referred for evaluation of multiple drug allergies that have
9 impaired her course of management for recurrent urinary tract infections. The patient had a
10 significant medical history of other drug allergies including allergies to: nitrofurantoin,
11 trimethoprim-sulfamethoxazole, penicillin G benzathine, sulfacetamide sodium, and
12 erythromycin, which have caused pruritus and rash immediately upon drug administration. The
13 patient was scheduled for penicillin skin testing, followed by another visit for an oral challenge
14 with amoxicillin performed on a separate day if skin testing were negative. The patient could not
15 recall when she last had a reaction to penicillin, but she noted being able to tolerate cefdinir.

16 During the first visit, both skin prick and intradermal tests with penicillin and
17 benzylpenicilloyl polylysine were negative when compared to a saline control (0 x 0 mm) and a
18 positive histamine control (10 x 12 mm). The patient left the office, but within less than an hour
19 after the negative skin test was read (Figure 1), she developed diffuse urticaria and pruritus
20 concentrated on her upper extremities, scalp, and groin. She immediately returned to the office
21 for reassessment.

22 The patient's baseline vital signs before skin testing included blood pressure of 116/74
23 mmHg, heart rate of 67 beats per minute, and respiratory rate of 16 breaths per minute. Upon

returning to the clinic, the patient presented with a blood pressure of 90/58 mmHg, heart rate of 99 beats per minute, SpO₂ of 92%, and respiratory rate of 21 breaths per minute. Fifty milligrams of diphenhydramine and 180 milligrams of fexofenadine were administered. The skin test sites remained negative. Five minutes later, she was still noticeable itchy and developed throat clearing and a new productive cough, at which point 20 mg of famotidine was given. Throughout the event, her lung sounds were clear to auscultation. Her repeat vitals were as follows: blood pressure of 100/60 mmHg, heart rate of 79 beats per minute, and SpO₂ of 98%. The patient was discharged when the pruritus fully resolved and vital signs returned to baseline. While at home three hours later, the pruritus returned with throat clearing, which prompted an emergency department visit. The patient was discharged home with a regimen of 50 mg diphenhydramine every six hours. She woke up the next morning with a complete resolution of symptoms (Figure 1).

The patient has a significant medical history of hyperlipidemia, hypertension, depression, hypothyroidism, and recurrent urinary infections. She was managed by daily metoprolol 100 mg, lisinopril 40 mg, simvastatin 20 mg, cefdinir 300 mg, levothyroxine 75 µg, citalopram 10 mg, and lorazepam 0.5 mg. Although epinephrine is the standard of care for anaphylaxis, considering the patient's combination of mild systemic symptoms, age, beta blocker and angiotensin-converting enzyme (ACE) inhibitor use, and comorbidities, epinephrine was withheld while the patient remained under observation. Her symptoms resolved with diphenhydramine and fexofenadine. Glucagon was not available in the clinic at the time.

Systemic reactions following a positive skin prick test and/or a positive intradermal test have been reported in the literature at a low prevalence rate. Swender et al. conducted a retrospective study to evaluate the rate of epinephrine administration after skin testing over a

period of thirteen years in a large suburban allergy/immunology office. Only six cases with skin prick tests and zero cases with intradermal tests required the use of epinephrine to manage systemic reactions. All six patients exhibited positive sensitization of skin prick tests of various types of allergens. This study demonstrated a rate of 20 per 100,000 skin prick tests (0.02%) that required epinephrine to manage systemic reactions. No epinephrine was needed to manage adverse reactions associated with intradermal tests.⁶

A common protocol for evaluating penicillin allergy is to perform a skin prick test followed by an intradermal test and if negative an oral challenge with amoxicillin.^{2,3} Skin testing with diluted penicillin and benzylpenicilloyl polylysine has a reported negative predictive value of 95%, which increases to 100% when followed by an oral amoxicillin challenge.⁷ A study by Pichichero et al. suggested the importance of evaluating penicillin hypersensitivity with a protocol of skin testing followed by an oral challenge, and repeat skin testing to ensure no re-sensitization through memory B cell expansion expressing IgE.⁸ A newer penicillin evaluating protocol has been proposed to bypass skin testing and directly invoke an oral drug challenge for low-risk individuals.^{4,5} Low risk criteria include penicillin associated symptoms of benign rash, gastrointestinal symptoms, headaches, and benign somatic symptoms that occurred more than twelve months ago or an unknown history of penicillin allergy. Criteria for excluding the direct oral amoxicillin challenge protocol include a reaction to penicillin within the past twelve months, a history of shortness of breath or anaphylaxis associated with penicillin, or a history of severe penicillin hypersensitivity of blistering rash with skin loss, hemolytic anemia, nephritis and hepatitis.⁴ Another study suggested that direct oral penicillin challenge is safe for individuals older than seven years with a history of non-life-threatening reactions to penicillin.⁵

Our patient's history of penicillin allergy fits the low risk reaction criteria previously proposed by Banks and Iammatteo since her reaction was more than 12 months prior, and her reaction history included only benign cutaneous symptoms. Nonetheless, despite this low risk history and negative skin test results, she experienced a mild systemic reaction with minimal penicillin exposure.

While there remains controversy with regard to the role of skin testing versus direct challenge in the evaluation of penicillin allergy, this case demonstrates that even a small exposure to penicillin in the form of skin testing may be the trigger for an anaphylactic reaction, and that patients may benefit from a longer post-testing monitoring period regardless of test outcome. Based on this experience, we support the traditional approach to a penicillin hypersensitivity skin testing followed by an oral amoxicillin challenge. Although a direct oral penicillin challenge has been associated with low rate of systemic reactions,^{4,5} the development of an anaphylactic reaction in our patient, even though mild, highlights the importance of skin testing prior to an oral challenge as a safety check to prevent fatal adverse reactions during the challenge. In addition, the use of beta-blockers and/or ACE inhibitors when used to treat other maladies may complicate the care of anaphylaxis not only in the biomedical sense but also in the perception to treat with epinephrine by the caregiver.⁹ This case also demonstrates that medications such as beta blockers and ACE inhibitors may increase the risk of systemic reaction due to their biomedical effects and care providers' impressions.⁹ Steps should be taken to change the medication profile, especially in the elderly, if there is a risk of anaphylaxis from known or unknown allergen. Herein, we present the first case of a systemic drug reaction following negative skin testing with penicillin and benzylpenicilloyl polylysine.

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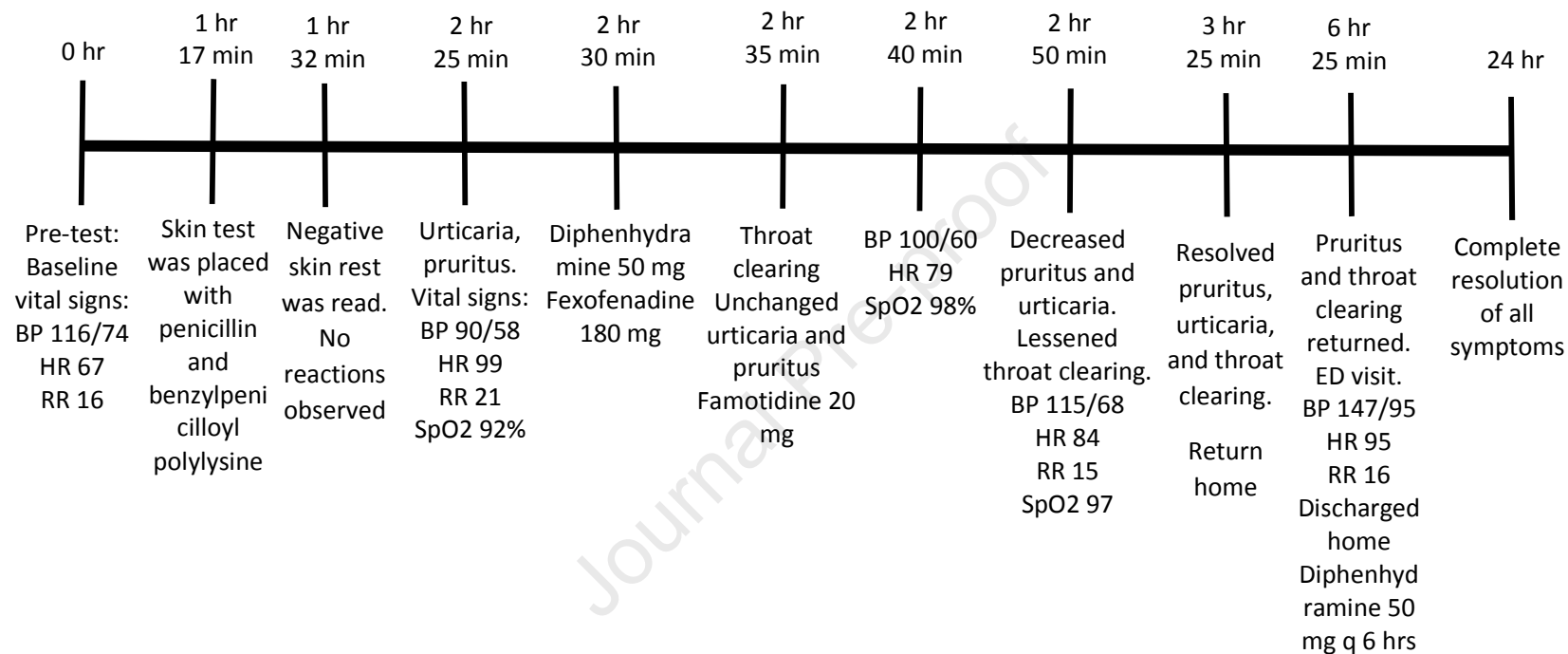
Figure 1:

Figure 1. Clinical timeline of the patient's anaphylactic reaction after a negative skin testing reading.