

## Assessment of the current practice of antibiotic skin testing in a tertiary Hospital in United Arab Emirates

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### Abstract

**Introduction:** Skin testing can be a useful diagnostic tool to identify patients who are allergic to penicillin. Procedures for skin testing in the United Arab Emirates have not been standardized. The aim of this study was to examine the current practice of antibiotic skin testing in a tertiary hospital in the United Arab Emirates (UAE).

**Methodology:** This was a prospective cross-sectional study conducted in Al Qassimi Hospital, in which the medical records of all patients who were prescribed antibiotics over an eight-week period were screened to evaluate patients' history, indication for performing the test, results, and documentation of findings.

**Results:** During the study period 357 patients received parenteral antibiotics, of which 238 had one skin test, 21 had two skin tests, and one patient had four skin tests. Skin testing was performed without regard for patient history. Documentation of both positive and negative results was poor. There was no standard technique for skin testing used within the institution, and significant variations were noted between wards. In most cases the techniques used deviated from recommended procedures in the medical literature.

**Conclusions:** Standardized guidelines for antibiotic skin testing should be established and implemented as soon as possible using recommended international guidelines.

**Key words:** antibiotic; skin test; penicillin; cephalosporin

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### Introduction

Since the introduction of penicillin as a therapeutic agent in the 1940s, there have been allergic reactions, including deaths, reported in patients using this beta-lactam antibiotic. In a retrospective study, one third of patients who died because of an anaphylactic reaction to penicillin were found to have histories of penicillin allergy [1]. A separate study found that 12.7% of inpatients reported a history of allergy to penicillin [2]. Given such data, physicians tend to practice excessive caution when using penicillin. In a review of studies on penicillin allergy, Solensky *et al.* reported that 33% of patients who were skin test positive in fact had a “vague history” (*i.e.*, poor documentation of antibiotic treatment or incomplete description of allergic reaction) of penicillin allergy [3]. However, many patients with histories of penicillin allergy can go on to take penicillin without any adverse reaction [4]. Even though patients with a history of penicillin allergy are more likely to have a positive skin test,

27.8% of patients with a convincing history of penicillin allergy were negative when tested for allergy [5]. There are several reasons for these results, as reviewed by Solensky [6]. The patient may have reported an allergy after receiving a combination of several drugs; the allergy was in fact to a non-beta-lactam; the allergic reaction might have been associated with the patient's disease state; or incorrect skin testing techniques may have produced a false positive result, and cause the patient to be mislabeled as penicillin sensitive.

If patients are suspected to have a penicillin allergy, alternative non-beta-lactam antibiotics, such as vancomycin or quinolones, tend to be prescribed [7,8]. The alternative therapies are likely to be broad spectrum [9] and more costly, placing a significant economic burden on the health system [9,10]. The skin test can be valuable for evaluating penicillin-resistance in critically ill patients who would otherwise be denied penicillin group antibiotics because of a suggestive history [11].

**Table 1.** Skin testing according to type of antibiotic

	Done	Not done	Total
Amoxicillin/Clavulanic acid	10	9	19
Cefotaxime	1	4	5
Ceftazidime	4	4	8
Cefuroxime	30	9	39
Ceftriaxone	161	32	193
Piperacillin/ tazobactam	62	32	94
Ciprofloxacin	0	12	12
Clarithromycin	1	2	3
Amikacin	0	18	18
Gentamicin	0	2	2
Tigecycline	1	5	6
Meropenem	11	26	37
Metronidazole	0	37	37
Streptomycin	0	1	1
Teicoplanin	2	5	7
Vancomycin	1	4	5

However, penicillin skin testing should not be done routinely for all patients. The United States Centers for Disease Control and Prevention recommends that the penicillin skin test is done only in patients with a history suggestive of penicillin allergy, using penicilloyl poly-lysine as the major determinant, penicillin G, penilloate and penicilloate as the minor determinant mixture, a negative control and a positive control of histamine [12]. The patient should not have taken antihistamines in the period prior to testing. Conversely, inappropriate choice of patient or the application of incorrect technique can cost treatment time and may put the patient at risk.

Penicillin skin testing is commonly performed in patients before receiving therapy with  $\beta$ -lactam antibiotics at our hospital. Our hospital is one of 17 public hospitals in the United Arab Emirates (UAE). Currently there are no guidelines from the UAE Ministry of Health regarding antibiotic skin testing, and no hospital has yet developed its own guidelines. This prospective cross-sectional study was performed to evaluate skin testing in inpatients at our hospital, with a focus on the indications for skin testing, the technique used, and the results. We anticipate that the results of this study could catalyze the development of a standard set of treatment guidelines in the UAE.

## Methodology

This study was reviewed and approved by the Institutional Research Ethics Committee (study number 082009) of Al-Qassimi hospital. The study was performed over a period of eight weeks from 1

October 2009 to 30 November 2009 at Al-Qassimi hospital, Sharjah, which is a tertiary hospital with 229 inpatient beds. Medical records of adult inpatients who had been prescribed a  $\beta$ -lactam antibiotic were reviewed. The hospital maintains a single written medical record for each patient. Laboratory results are made available in an electronic format; however, a hard copy is also printed and inserted into the patient's file. For each antibiotic prescribed information was collected on previous history regarding antibiotic allergy, immune status of the patient, whether or not a skin test was done and the result of the skin test if applicable, technique of the skin test, and documentation of the results. Previous history was considered to be negative if there was a clearly documented negative skin test, if there was previous use of a  $\beta$ -lactam antibiotic documented, or if "no known allergy" was documented in the file. Patients with no mention of allergy and no previous use of the antibiotic were considered to have "unknown penicillin allergy status". The data was analyzed using Chi-square tests for the differences between population proportions based on two or more samples. Significant differences were tested at 5% significance level.

## Results

During the study period there were 1,046 admissions, and a total of 1,271 inpatients (351 males and 920 females). We identified 486 prescriptions of antibiotics dispensed to 357 patients whose mean age was  $40.29 \pm 17.5$  years. A total of 284 skin tests were

**Table 2.** Differences in performing antibiotic skin test between wards

Ward	Skin test done		Skin test not done	Total
	Physician's request	Done without request		
Intensive care unit	0	8	26 (76%)	34
Coronary care unit	0	9	49 (85%)	58
Cardiac intensive care unit	0	11	16 (59%)	27
Medical ward 1	0	32	20 (38%)	52
Medical ward 2	2	30	26 (45%)	58
Surgical ward 1	6	77	13 (14%)	96
Surgical ward 2	2	35	8 (18%)	45
Maternity ward 1	23	32	20 (27%)	75
Maternity ward 2	5	12	24 (59%)	41

performed, 38 of these based on a physician's request and 246 based on the judgement of nurses as part of their standard care practice. There was no record of an allergic type reaction in any patient tested. Of the 357 patients in the study 238 received one skin test, 21 patients received two tests, one patient received four tests and the rest received no skin test.

Antibiotics from different classes were used during the study. Table 1 shows that while aminoglycoside administration was not preceded by skin testing, allergy testing for some other non  $\beta$ -lactam antibiotics such as clarithromycin and teicoplanin was performed.

#### History

Three patients had a documented clinical history of penicillin allergy; two patients provided a verbal indication of penicillin allergy; and one patient provided a verbal history to erythromycin allergy. In all six cases the nature of the reaction was not known. A skin test was performed for all these patients. None of the skin tests indicated an allergy to the respective antibiotics; however, only one patient had the result documented in the medical records.

#### Indication

Within the hospital, there was no common policy for administration of the antibiotic skin test, resulting in significant variations in test application among surgical wards (Table 2). The lowest incidence of skin testing was in critical care areas and one of the two maternity wards ( $p = 0.00002$ ). In all wards skin testing without a physician's request was significantly more frequent than performing the test

following a physician's order ( $p = 0.00001$ ). For the skin tests performed, multiple comparison tests of two proportions show that the maternity wards had significantly lower rates of performing the test in the absence of a physician's request ( $p = 0.019$ ). It is not the policy of any ward to perform the skin test only if a physician has requested it. On the other hand, the intensive care unit and coronary care unit were the wards most likely not to perform the testing, while the surgical wards were most likely to perform the test ( $p = 0.001$ ).

#### Documentation and follow-up

Of all the skin tests done only two were interpreted as giving a positive result (both with piperacillin/tazobactam) and a third patient who showed a positive skin test result to cefuroxime went on to receive the same antibiotic with no adverse reaction. This latter result indicates that either the patient's reaction was not due to the antibiotic tested or the interpretation of the skin test was incorrect.

Five out of six patients who reported a history of allergy yet had a negative skin test did not have this result documented in their medical records. The fact that the patients went on to receive the antibiotic indicated that the skin test result was negative. It could also mean, however, that no one checked the record prior to administration of the antibiotic.

#### Skin test protocol/technique

No common protocol was implemented in the hospital with respect to when and how to perform antibiotic allergy testing. In all cases the same medication that was prescribed and due to be given

was used to perform the intradermal skin test. Dilutions varying from 10 fold to 100 fold of the reconstituted solution were prepared. Different volumes varying between 0.05 mL and 0.01 mL were injected intradermally into the volar area of the forearm. Neither positive nor negative controls were used. Results were read by the physician or nurse 15 minutes later. Documentation of the skin test being performed was noted on the medication chart or in the nursing notes; in both cases this documentation was not easily recognizable so was of limited use for future reference.

## Discussion

This study has highlighted some important findings regarding the current practice of antibiotic allergy testing in a clinical setting. History of allergy to antibiotics has been reported in 0.7% to 10% of hospital inpatients [13]. In our study only five (1.4%) of the 357 patients had a history of penicillin allergy. Many patients did not know or did not remember the type of reaction they developed to penicillin. Patients with allergy to penicillin lose their sensitivity with time, as demonstrated by a negative penicillin skin test. The lower incidence of positive history of penicillin allergy we observed could be due to the lack of clear documentation in the patients' records. Despite the fact that a positive history was noted in only three cases, 335 patients (65%) received at least one skin test.

All three patients with a history of allergy to antibiotics and who were skin test negative received the same antibiotics (two of them ceftriaxone and one tigecycline) with no adverse effects. This observation is in agreement with reports in the literature that most patients who have a history of being allergic to penicillin-type drugs can in fact go on to receive the drug safely [4,14].

Recommendations for performing the intradermal penicillin skin test are to use penicilloyl-poly-lysine (PPL, also known as the major determinant) and a combination of benzylpenicillin, sodium benzyl penicilloate and benzylyl penicilloic acid (the minor determinant mixture, or MDM), a negative control and a positive control [15,16]. When skin tests are performed with the major and minor determinants, the positive predictive value is 50% and the negative predictive value is 97-99% [17]. Gadde *et al.* found that about 75% of patients who react on penicillin skin tests react to penicilloyl polylysine [14]. Skin testing with major and minor penicillin determinants is safe and important to protect a truly allergic patient

from anaphylactic reaction [4]. While benzylpenicillin can partially compensate for PPL and MDM unavailability, more than 20% of true allergies will be missed if the major and minor determinants are not included in the diagnostic protocol [18]. Although the technique for the skin test has been standardized, this technique is not being implemented in our setting. This puts into question the validity of the results of the skin test under our current hospital conditions.

Cephalosporin allergy in patients with a history of penicillin allergy has been estimated to range between 1% and 16%, depending on the generation of the cephalosporin [19]. There is no validated method for performing a skin test for cephalosporins. A recent study evaluating immediate allergic reactions to cephalosporins in non-penicillin allergic patients showed that positive reactions generally implied allergy, while negative reactions required confirmation with an oral challenge, since 50% of those testing negative went on to have a reaction in response to the oral form of the cephalosporin [20].

In our study only three patients had positive skin tests. Two of these were to piperacillin/tazobactam and the third was to cefuroxime. The patient who tested positive for cefuroxime still went on to receive the medication without consequence.

The data that was obtained regarding the technique used for the skin test showed that different concentrations and volumes of the injected solutions were used. The skin test solutions being used were not validated solutions and were invariably diluted solutions of the drug prescribed for the patient. Injecting large volumes can elicit a non-immune reaction. Furthermore, in the absence of a negative control, a proper evaluation of the result of the skin test cannot be made. While the time interval until the results were read was consistently 15 to 20 minutes, the way in which the result of the skin test was interpreted was ambiguous and not consistent between wards. Similarly, a study [21] in which 12 Korean hospitals were surveyed regarding their practice of antibiotic skin testing similarly found that volumes injected were up to ten times those recommended, and that interpretation of the test result was not consistent among the hospitals. The results of the Korean study are similar to ours in that there was a lack of guidelines on antibiotic skin testing, and as a result there was no uniformity in the practice among the different hospitals. In our study we observed a lack of uniformity in testing practice in the same hospital, among different wards.

Documentation of the results of the antibiotic skin test is important to identify patients who are candidates for the skin test in future, and to avoid unnecessary skin testing. In our study we found poor documentation of the results. Similar findings were reported by Warrington *et al.* [22] in a study in which 49% of patients were still labeled as penicillin allergic despite having negative skin tests or an uneventful drug challenge. Poor documentation could be expected to be associated with discrepancies between the medical record and the allergy history [7]. Mislabelling of patients as allergic leads to selection of broad spectrum or more expensive medications.

This study demonstrated that in the absence of a policy for antibiotic skin testing, application of the procedure is haphazard and may be performed when it is not indicated for a particular patient or a particular antibiotic. Furthermore, when the test is done, it is not done using a proper technique, nor are the results documented in the patients' medical records. There is an urgent need to develop and implement a comprehensive, uniform protocol for antibiotic skin testing in the UAE.

## Conclusion

Although the majority of patients were given at least one allergen skin test, due to the technique used to perform the skin test, our patients should be considered as patients receiving antibiotics with no skin test. Our results confirm that many patients with a history of penicillin allergy can receive  $\beta$ -lactam antibiotics safely. Our study also identifies a malpractice of performing skin tests, especially when they are not done correctly, to give a false assurance that subsequent antibiotic administration will be safe. Health institutions should have an antibiotic skin test policy that is implemented consistently throughout the hospital.

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