

Evaluation of immediate reactions to β lactam antibiotics using a comprehensive diagnostic protocol

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ABSTRACT

Background: β lactam antibiotics are commonly prescribed groups of antibacterial drugs for various infections however the prevalence of its allergic effects is not clear in our country, hence the need for an effective diagnostic protocol to determine immediate hypersensitivity reactions. The objective was to formulate a diagnostic protocol for evaluating immediate drug hypersensitivity to β lactam antibiotics.

Methods: A prospective study was conducted at a tertiary care hospital. Adults who were prescribed any class of β lactam antibiotic were included. Non irritating concentrations of the antibiotic as per The European Network on drug Allergy were used. A strict three step diagnostic algorithm with skin prick test followed by intradermal test and drug provocation test, with 20 minutes observation period between each step, to determine cutaneous allergic reactions was followed.

Results: The most commonly prescribed drug was cefazolin, followed by ceftriaxone, and cefoperazone + sulbactam combination. The culprit drugs were ceftriaxone in 4 (4.7%) patients, followed by piperacillin + tazobactam combination in 3 (3.5%), amoxicillin + clavulanic acid in 2 (2.3%) and 1 (1.1%) each for cefotaxime and cefepime + tazobactam combination. No patients were positive for skin prick test; 2.4% were positive for intradermal test and 10.6% were positive for drug provocation test.

Conclusions: This diagnostic protocol is apt to adequately diagnose immediate reactions to β lactam antibiotics and henceforth can be used effectively in India. However, the skin prick test may be excluded but the intradermal test and drug provocation test is crucial to identify these immediate reactions.

Keywords: Adverse drug reactions, β lactam antibiotics, Drug hypersensitivity, Drug allergy, Drug provocation test, Skin prick test

INTRODUCTION

Drug hypersensitivity is an immune mediated reaction to a drug which can present with symptoms as mild as itching to a severe reaction like Steven Johnson syndrome.¹ These reactions are unpredictable and are not dose dependent. It can be described as two types; immediate and delayed, based on the time interval between the administration of the drug and the onset of signs and symptoms.² Specifically, immediate reactions are evidenced by a local or generalised response that begins within a few minutes to about an hour after exposure to a drug due to release of inflammatory mediators by mast cells or basophils. Many

drugs can facilitate this release either directly (anaphylactoid reaction) or through IgE-specific antibodies.³ Thus, prompt identification of the adverse reactions, withdrawal of the drug and treatment of its effects is of utmost importance.

The primary focus of most studies revolves around determining the incidence of adverse drug reactions rather than specific drug allergy.⁴ β lactam antibiotics are some of the most commonly prescribed group of drugs for various bacterial infections, though the prevalence of its allergic effects is unknown.⁵ This class of drugs includes penicillin and its derivatives, cephalosporins, monobactams, carbapenems and carbacephems.

There are a few studies which have administered safe and non-irritating drug concentrations to various drugs using minimally invasive skin prick tests to evaluate drug hypersensitivity.^{6,7} Hence, there is a need for a simple yet effective diagnostic protocol to determine these reactions as it could prevent severe complications, which are easily avoidable.

Various epidemiological studies state the incidence of ADRs considering all classes of drugs. Global incidence of ADRs accounts for 3 to 6% among hospital admissions and 10 to 15% of hospitalized patients.⁸

There are studies which describe the pattern of adverse drug reactions including all classes of drugs which states that in India, incidence of ADR is between 5.9 to 22.3% while deaths due to ADRs account for 1.8%.⁹ A study by Rehan et al, describing the trends of adverse drug reactions in a tertiary care hospital reports the incidence of drug allergy and it was found that Antimicrobials (35.7%) were the main cause of ADRs and the most common ADR manifestations were attributed to the cutaneous system (40.4%).¹⁰

Among antimicrobials, β lactam antibiotics are commonly used and are prescribed to most of our patients irrespective of their allergy status. There is a lack of guidelines and standardisation of skin tests to detect immediate hypersensitivity reactions to β lactam antibiotics.¹¹ Apart from a detailed medication history, cutaneous tests are mainly implemented for immediate reactions, primarily, skin prick or puncture tests.¹² Intra-cutaneous tests have been used in patients who have lower sensitivity to skin prick tests. Drug provocation tests provide definite diagnosis wherein drugs are given either as oral challenge tests, as per full dose prescribed by the physician or organ challenge to clarify the role of allergens associated with specific organs.^{13,14}

The European Network on drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) Interest Group on Drug Allergy have published guidelines and position papers on techniques, procedures, diagnostic approach to skin testing, drug provocation tests as well as recommendations for the management of β lactam hypersensitivity.¹⁵ They have proposed the use of Non irritating Concentrations (NIC) and a step wise diagnostic protocol to approach antimicrobial immediate hypersensitivity reactions, which have been validated via trials on their population.¹⁵⁻¹⁸

Objective of the study was to formulate a diagnostic protocol for evaluating immediate drug hypersensitivity to β lactam antibiotics.

METHODS

On approval, a written informed consent was obtained from the patients explaining in detail about this study.

A prospective study was conducted in a tertiary care hospital in Bangalore, India. Inpatients from all departments who were prescribed with β lactam antibiotics were selected for administration of the protocol. All patients above the age of 18 years who have been prescribed any class of β lactam antibiotic were included in the study. Patients who had a previous history of hypersensitivity to β lactam antibiotics, clinically diagnosed immunocompromised states and patients who require prompt antibiotic administration admitted in intensive care units were excluded from the study.

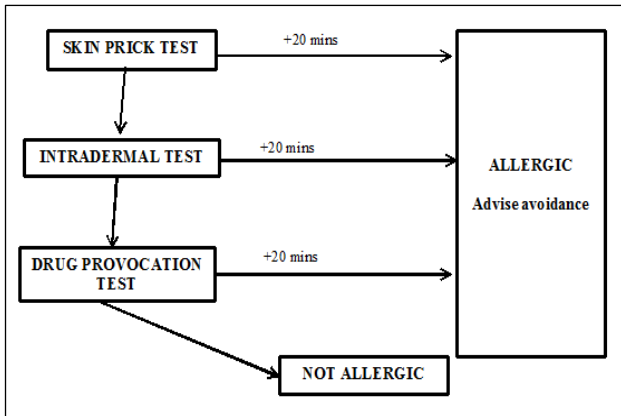
Based on a previous study conducted by Bousquet PJ et al, it was observed that the hypersensitivity due to β lactam antibiotics as confirmed by skin testing was found to be 69.3%.¹⁹ In the present study, expecting a similar result by skin tests, sample size was estimated considering a relative precision of 15% and desired confidence level of 95% which worked out to be 76 subjects.

The study was conducted at a tertiary care hospital in Bangalore, India. Around 187 patients from various specialities, mainly, Obstetrics and gynaecology, Surgery, General Medicine, Orthopaedics, Urology and Gastroenterology were screened and 85 patients were included in the study based on the inclusion criteria.

Socio demographic details were obtained from the patients with the help of a questionnaire form. Additionally, detailed history was obtained regarding nature of illness, drug prescribed, route of administration of the drug, prescribed dosage, duration of the treatment, concurrent use of other classes of drugs, past and family history of drug and food allergy.

In this study, NIC of the various classes of drugs under β lactam antibiotics such as penicillins, cephalosporins, monobactams and carbapenems were prepared according to pre - set dilutions as ENDA. The recommended doses for penicillin group were benzyl penicillin 10,000 IU and other penicillins 20mg/dl at 1:10 dilution; cephalosporin group were cefazolin at 33mg/ml at 1:10 dilution and other generation cephalosporins at 2-20mg/ml at 1:10 dilution; monobactam and carbapenem group were aztreonam 2mg/ml, imipenem 0.5-1mg/ml and meropenem 1mg/ml.^{16,20}

For each patient, the prescribed β lactam antibiotics were diluted to its respective minimum dose as per ENDA and administered according to the protocol, prior to the initiation of the full course. Distilled water was used as a diluent. Once diluted, a strict protocol was followed (Figure 1) where in the NIC of the respective drug was initially administered to the patient using a skin prick test using lancets, followed by an intradermal test using an insulin syringe keeping an observation period of 20 minutes between each test. The next step in this protocol was to administer a drug provocation test with the full dosage as prescribed by the physician.



The stepwise approach in diagnosing reactions to β lactam antibiotics

Figure 1: Diagnostic algorithm for the diagnosis of immediate reactions to β lactam antibiotics.¹⁶

Since there are no established protocols to test immediate hypersensitivity reactions to β lactam antibiotics in our country, the NIC as per ENDA for this study group were used as an initial test dose concentration. Both localised and generalised reactions in the form of primary signs and symptoms like pruritic, rash, urticaria (skin manifestations), nausea, vomiting, abdominal cramps (gastrointestinal manifestations), bronchospasm, laryngeal oedema and anaphylaxis with hypotension (cardiorespiratory manifestations) were considered as positive reactions and an absence of these reactions were considered to be negative.³ A positive reaction at the respective step was noted down. If there was no reaction to the drug in all the three steps, the patients were termed as non-allergic and the full course of the antibiotic was continued.

RESULTS

In this study, total of 85 patients were recruited and the strict protocol was followed. The population comprised of 43 males (51%) and 42 females (49%) as seen in Table 1. Among these, 6 males and 5 females were found to be positive for immediate reactions.

Minimum age of the patient group was 18 years old and the maximum age was 79 years, with a mean age of 42.76 ± 7.78 years. The age distribution of the patients has been depicted in Table 1.

Among these patients, the most commonly prescribed β lactam antibiotics, in order were cefazolin (26), ceftriaxone (23), cefoperazone + sulbactam combination (8), cefotaxime (7), cefuroxime (7), piperacillin + tazobactam combination (6), cefepime + tazobactam combination (3), ceftriaxone + sulbactam combination (3) and amoxicillin+ clavulanic acid combination (2). The monobactam and carbapenem groups were not frequently used in the inpatient setting as the first choice of drug. However, they were prescribed in the Emergency Medicine department, but this strict protocol could not be followed due to the necessity of prompt administration.

Table 1: Age distribution of patients.

Age range (in years)	Number of patients (n)	Male	Female	Percentage total (%)
18-27	19	08	11	22.35
28-37	20	05	15	23.50
38-47	14	09	05	16.47
48-57	10	08	02	11.77
58-67	12	06	06	14.11
68-77	09	06	03	10.59
78-87	01	01	00	01.18
Total	85	43 (51%)	42 (49%)	100
Mean Age \pm SD	42.76 ± 7.78			

A total of 11 patients (13%) were found to be allergic as per the protocol. None of these patients were found to be positive after the skin prick test was administered. However, out of 11 patients, 2 patients showed positive reaction to the intradermal test and 9 patients were positive only to the full dose provocation test.

Table 2: Immediate hypersensitivity reactions with respect to steps in the diagnostic protocol.

Drugs	Skin prick test	Intradermal test	Drug provocation test	Total number of patients
Ceftriaxone	0	1	3	4
Piperacillin + Tazobactam	0	0	3	3
Amoxicillin + Clavulanic acid	0	0	2	2
Cefotaxime	0	0	1	1
Cefepime + Tazobactam	0	1	0	1

On analysis of immediate reactions to each drug, we observed that among the allergic patients, 4 were positive for ceftriaxone, 3 for piperacillin + tazobactam

combination, 2 for amoxicillin + clavulanic acid, 1 for cefepime + tazobactam combination and 1 for cefotaxime. Among these drugs, ceftriaxone and cefepime +

tazobactam combination were found to be positive at the intradermal stage for two patients and the rest were positive for full dose provocation test, as depicted in Table 2.

Most common immediate drug reactions to β lactams following drug provocation test observed in this patient group was itching and rash as shown in Table 3.

Table 3: Adverse drug reactions following drug provocation test.

Drug	Age of the patient (in years)	Drug reaction	Number of patients
Piperacillin +Tazobactam	31	Itching+rash	3
	40	Itching+giddiness	
	54	Itching+nausea	
Ceftriaxone	25	Rash	3
	40	Rash+breathlessness	
	46	Itching+rash	
Amoxicillin + Clavulanic acid	26	Itching+rash	2
	29	Itching+blister	
Cefotaxime	19	Rash	1

DISCUSSION

This study mainly focussed on arriving at a simple and effective diagnostic protocol to evaluate immediate reaction to β lactam antibiotics in view of safety of the patients and better compliance. Currently, there is a lack of standardised guidelines for testing hypersensitivity and the minimum concentration of the drug required for the same. Hence, the NIC as per ENDA was followed to study its relevance in our population.

In this study population, the male to female ratio was 1.02:1. There was no association observed between gender and its relation to immediate hypersensitivity reaction to β lactam antibiotics. A similar study was conducted by Sullivan et al, where allergies to penicillin were tested, and there was no influence of gender on immediate reactions to penicillin group (males 49.3% and females 50%).²¹

Patients aged above 18 years were included in this study, with mean age of 42.76 \pm 7.78 years. In comparison, a study conducted by Bousquet PJ et al, which also followed the ENDA recommendations to test allergic reactions to β lactams, also included adults with a median age of 32 years.¹⁹ A meta-analysis conducted by Harandian et al, has concluded that the prevalence of allergy to penicillin groups is more in adults (7.78%) when compared to children (1.98%).²²

It was also observed that all patients who were allergic to β lactam antibiotics were less than 56 years of age. This is probably because the rate of true positive results in penicillin skin testing are in fact lower in the older age

group.²² The study by Sullivan et al has also observed higher prevalence of penicillin allergy in young adults than compared to elderly.²¹

In this study, the most commonly used drug was cefazolin, followed by ceftriaxone, and cefoperazone + sulbactam combination. On analysing the data, it was observed that the most common immediate hypersensitivity reaction was for ceftriaxone, followed by piperacillin + tazobactam combination, amoxicillin + clavulanic acid as shown in Table 2. In association to this, the study by Rehan et al, has observed that out of total 520 ADRs, 186 (35.7%) were due to antimicrobials. Amongst these antimicrobials, ceftriaxone allergy was seen in 47 subjects followed by amoxicillin + clavulanic acid in 30 subjects.¹⁰ Another study by Arulmani et al in which adverse drug reactions were monitored in a secondary care hospital, in South India showed that out of total 164 patients, allergic reaction to ampicillin was seen in 18 subjects (10.9%) and to that of cefotaxime in 10 subjects (6.1%).⁹ In a similar study by Doña I et al, amoxicillin + clavulanic acid was most commonly used (8.7%) followed by penicillins (3.98%) and cephalosporins (1.5%).²³ In a recent study, it was found that amoxicillin was the culprit drug in 50%, followed by 12% each for penicillin and cephalosporins.²⁴

Variations in occurrence of allergy in the form of immediate reactions to β lactams were observed. In this study total, allergic patients were 13% and non-allergic were 87%. In a similar study by Ratzon et al, 25 out of 49 patients (51%) were tested positive for immediate reactions to β lactam group of antibiotics.²⁴ In another study by Doña I et al, the immediate allergic reactions to β lactams ranges from 21.19% in 2005 to 16.07% in 2010.²³

Skin tests include two steps: skin prick test followed by intradermal test. In this study it was observed that, among the β lactam antibiotics tested, there were no positive reactions to the skin prick test. A skin prick test was used as the first step in the diagnostic algorithm as per ENDA guidelines. Many studies have utilized the skin prick test in different dilutions in order to identify immediate reactions to β lactam antibiotics.^{19,25} A study by Sullivan et al has utilized skin tests in the detection of penicillin allergy only, wherein a total of 63% of patients tested positive and out of these, 57.2% were inpatients.²¹ Another study by K. Lammintausta et al, assesses the usefulness of skin tests to prove drug hypersensitivity. Among the many tests used here, skin prick tests were used for all classes of antimicrobials and it was observed that only 0.7% were positive for skin prick test to β lactam group.²⁵ Since, none of the patients tested positive for the skin prick test, this step is probably can be omitted for future diagnostic algorithms.

This study revealed that 2 out of 85 patients were found to be positive and they manifested as wheal and flare (cefepime + tazobactam) and localised itching (ceftriaxone). In a similar study by K Lammintausta et al, intradermal test was administered with penicillin test

substances in 31 patients and no positive reactions were observed.²⁵ In another study by Sogn et al, 18% of patients tested positive for immediate hypersensitivity reactions for penicillins, as tested by both skin prick and intradermal tests together.²⁶

This study also revealed that 9 out of 85 patients were positive only after administration of full dose of the prescribed antibiotic. Among these patients, itching with rash was seen in 4 patients, only rash in 2 patients, and one patient each for itching with giddiness, itching with nausea and breathlessness with rash. A study by Bousquet PJ et al tests the requirement of oral challenges in the diagnosis of β lactam hypersensitivity where in a full dose provocation test was provided to all those patients who were negative for initial skin tests (both skin prick and intradermal tests) and out of 961 total patients, 783 (81.4%) patients were negative for skin prick test. Among those patients who tested negative for skin tests, 79 (10% of 783) were positive for drug provocation tests. Furthermore, amongst positive drug provocation, 52 (65.8%) involved a penicillin and 27 (34.2%) a cephalosporin.¹⁹

According to this study, among patients who presented with itching as one of the reactions following drug provocation test, the class of drug involved in order was, piperacillin + tazobactam (3), amoxicillin + clavulanic acid (2) and ceftriaxone (1) with both dermatological and systemic manifestations as shown in Table 3. In a similar study by Ratzon et al, 23 (88%) of the patients showed skin manifestations following a short drug provocation test.²⁴

In this study, the diagnostic algorithm was applied to the most commonly prescribed drugs. It has also been suggested that in case of a negative skin test, confirmation of drug allergy can be successfully achieved by challenges via oral or any other route.²⁵ There is a need for standardisation of guidelines to adequately identify these immediate reactions to antibiotics to help physicians in choosing safe drugs for their patients which in turn leads to better patient compliance. These simple, minimally invasive tests will also help prevent wastage of drugs and alleviate economic burden over the patients. This diagnostic protocol can be adequately used in an Indian setup to determine immediate reactions to β lactam antibiotics and can probably be followed with exclusion of the skin prick test.

This study revealed that adults were more prone to develop immediate reactions which mainly manifested dermatologically. Ceftriaxone was found to be a leading culprit drug among the cephalosporin group and piperacillin + tazobactam combination among the penicillin group. This diagnostic protocol is apt to adequately diagnose immediate reactions to β lactam antibiotics. However, the skin prick test may be excluded from it as no patients were positive to this step according to this study. The intradermal test followed by drug provocation test is crucial in identifying immediate reactions. It is essential to monitor the patient intensively

whenever drug provocation test is done as frequency of immediate reactions is high at this stage of the diagnostic protocol.

There are certain limitations to this study. This diagnostic protocol could have been followed up with a diagnostic protocol to determine delayed reactions to β lactam antibiotics in patients who were negative to the immediate hypersensitivity diagnostic protocol in order to adequately determine hypersensitivity to this class of drugs. Ig E levels could have been estimated to correlate with the immediate reactions.

Most studies quoted in this paper have shown positivity to the skin prick test in varying percentages. The reason for no positive reaction to this step seen in our study could probably be related to ethnic factors and drug concentrations. Hence future studies can be incorporated to explore these aspects.

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