

TABLE I. Nonirritating concentrations for 15 commonly used antibiotics

Antimicrobial drug	Full-strength concentration	NIC (as dilution from full-strength concentration)	No. of patients tested
Cefotaxime	100 mg/mL	10 ⁻¹	25
Cefuroxime	100 mg/mL	10 ⁻¹	25
Cefazolin	330 mg/mL	10 ⁻¹	25
Ceftazidime	100 mg/mL	10 ⁻¹	25
Ceftriaxone	100 mg/mL	10 ⁻¹	30
Tobramycin	80 mg/2 mL	10 ⁻¹	25
Ticarcillin	200 mg/mL	10 ⁻¹	25
Clindamycin	150 mg/mL	10 ⁻¹	25
Gentamicin	40 mg/mL	10 ⁻¹	30
Cotrimoxazole	80 mg/mL	10 ⁻²	25
Levofloxacin	25 mg/mL	10 ⁻³	25
Erythromycin	50 mg/mL	10 ⁻³	25
Azithromycin	100 mg/mL	10 ⁻⁴	30
Nafcillin	250 mg/mL	10 ⁻⁴	25
Vancomycin	50 mg/mL	10 ⁻⁴	30

Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics

To the Editor:

Care and treatment of the drug-allergic patient is challenging because there are few reliable methods available to detect the presence of IgE antibodies to most antibiotics. Except for penicillin, the clinically relevant antigenic determinants are not known and thus, diagnostic agents have not been developed.

Although no validated diagnostic tests are available for most antibiotics, the elicitation of a positive skin test result at a free drug concentration that is known to be nonirritating suggests that drug-specific IgE antibodies may be present. In this report, which is an extension of previous work done by our group,¹ we sought to determine nonirritating intradermal skin test concentrations for several different antibiotics and to present the data in a way that makes preparation easy in an office setting. Although there are numerous case reports of skin testing with antibiotics in their native form in selected patients,²⁻¹⁰ this report is the first to systematically evaluate the nonirritating skin test concentrations for several common antibiotic agents.

Study subjects included at least 25 healthy adult male and female individuals (18 to 50 years of age) who had no history of drug allergy. This study was approved by the Institutional Review Board at University of Texas Southwestern, and informed consent was obtained from all individuals tested.

Fifteen commercial parenteral antibiotics, approved for human use, were evaluated. These antibiotics, if in lyophilized form, were reconstituted according to the instructions in the package insert to their full-strength intravenous concentrations. Either saline or sterile water was used as the diluent, as recommended by the manufacturer. The full-strength concentrations of the drugs used are presented in Table I. All reagents were prepared fresh on the day of testing.

Approximately 0.02 mL of each drug dilution was injected intradermally into the forearm/arm in duplicate.

The wheals were measured immediately and again after 15 minutes. A 2 × 2-mm increase in wheal diameter over baseline was considered an irritant skin test response. A histamine positive control (1 mol histamine) and a saline negative control also were placed. The nonirritating concentration (NIC) for each antibiotic was obtained in a single subject initially. After the drug was prepared at the full-strength concentration, serial 10-fold dilutions were prepared and tested in this individual to determine the lowest dilution that did not elicit an irritant response. This concentration was then termed the NIC. After establishing the NIC for each antibiotic in this particular individual, a second group of individuals was tested with the NIC and with 1 or more 10-fold dilutions if necessary. The goal was to establish the highest concentration of drug (lowest 10-fold dilution) that would not elicit an irritant skin test response in all individuals tested.

Table I lists the NIC of the 15 antibiotics evaluated. Drugs that were nonirritating at a 10-fold dilution from full-strength were all 5 cephalosporins, tobramycin, ticarcillin, clindamycin, and gentamicin. Trimethoprim-sulfamethoxazole (TMP-SMX) was nonirritating at a 100-fold dilution; levofloxacin and erythromycin at a 1000-fold dilution, and nafcillin, vancomycin, and azithromycin at a 10,000-fold dilution from full strength. Only one of the subjects had a positive skin test response to any of the antibiotic dilutions outlined above. That subject, who had a history of sulfamethoxazole exposure but who had no history of a reaction, had a wheal and flare reaction to TMP-SMX at a 1000-fold dilution of the drug (0.08 mg/mL SMX). It is possible that this individual had TMP-SMX-specific IgE antibodies, since she did have a prior history of drug exposure. It is also possible that the response demonstrated was irritant in nature. The patient refused further testing with additional dilutions and refused drug challenge.

Ciprofloxacin at a 100-fold dilution elicited a markedly positive intradermal skin test response in all subjects tested. We were unable to determine the nonirritating concentration for this antibiotic because the irritating concentration ranged by 1000-fold in several subjects on separate testing dates.

In this report, we have determined the nonirritating skin testing concentration for 15 commonly used antibiotics. This study was designed to help the practicing allergist evaluate patients with histories of drug-induced reactions that have features consistent with an IgE-mediated process. We elected to use 10-fold dilutions of the full-strength reconstituted drug rather than expressing concentrations in milligrams per milliliter or moles per liter so that drug concentrations could be easily prepared in the office setting. The NIC was the highest drug concentration at which none of the tested subjects reacted. Ten-fold dilutions were chosen because of ease of preparation and convenience for the practicing physician.

We do not have an explanation for the wide variance in skin test responsiveness to the ciprofloxacin. Despite our inability to establish a nonirritating concentration for ciprofloxacin, we did establish that a 100-fold dilution is irritating in all subjects.

The antibiotic dilutions we have described are simple to prepare, and skin testing with them can provide the allergist with practical information. A positive skin test using the NIC of a drug suggests that the patient has drug-specific IgE antibodies and, for that reason, is at risk for urticaria, angioedema, and even anaphylaxis. On the other hand, a negative skin test result does not rule out the presence of drug-specific IgE antibodies. However, if intradermal skin testing is performed, the total amount of drug injected can easily be calculated and, as suggested in the recent drug allergy practice parameter, this dose may be used as a starting point for desensitization.¹⁰

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