

Drug desensitization

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The term *drug allergy* is loosely applied to many drug reactions. Consequently, when properly evaluated, most patients who are labeled allergic are found to lack hypersensitivity and are able to tolerate the implicated medication. A proportion of patients who undergo a thorough evaluation by allergists/immunologists are determined to be drug allergic. Although the usual recommendation for allergic patients is to avoid the medication in question, some clinical situations may necessitate re-administration. This article focuses on the approach to drug-allergic patients when administration of the sensitizing drug, or a cross-reacting one, is required.

Classifications and definitions

Adverse drug reactions are broadly categorized into predictable (type A) and unpredictable (type B) reactions [1]. Predictable reactions are more common and account for approximately 80% of all adverse drug reactions [2]. They are usually dose dependent, are related to the known pharmacologic actions of the drug, and occur in otherwise normal individuals. Unpredictable reactions are generally dose independent, are not related to the pharmacologic actions of the drug, and occur in susceptible individuals only. Representative examples of predictable and unpredictable adverse drug reactions are shown in Table 1.

Allergic drug reactions are also known as hypersensitivity reactions and account for approximately 6% to 10% of all adverse drug reactions [2]. Allergic drug reactions are distinguished from other unpredictable adverse drug reactions in that they are mediated by an immunologic mechanism. No single classification scheme permits the classification of all allergic drug reactions. Some allergic drug reactions can be classified using the Gell and Coombs hypersensitivity reaction scheme [3]. In this system, there are four types of hypersensitivity reactions: (1) immediate reactions mediated by IgE antibodies leading to mast cell and

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Table 1
Classification of adverse drug reactions

Type of reaction	Examples
Predictable	
Overdosage	Acetaminophen — hepatic necrosis
Side effect	Albuterol — tremor
Secondary effect	Clindamycin — <i>Clostridium difficile</i> pseudomembranous colitis
Drug-drug interaction	Terfenadine/erythromycin — cardiac arrhythmia
Unpredictable	
Intolerance	Aspirin — tinnitus (at usual doses)
Idiosyncratic	Dapsone — hemolytic anemia in G6PD-deficient patient
Allergic	Penicillin — anaphylaxis
Pseudoallergic	Radiologic contrast media — anaphylactoid reaction

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

basophil degranulation (type I), (2) cytotoxic IgM- or IgG-mediated reactions against a cell surface (type II), (3) immune complex deposition reactions with activation of complement (type III), and (4) delayed T lymphocyte-mediated reactions (type IV). Some drugs are capable of causing more than one type of Gell and Coombs reaction. For example, treatment with penicillin can result in anaphylaxis (type I), hemolytic anemia (type II), serum sickness-like reaction (type III), and contact dermatitis when applied topically (type IV).

Some allergic drug reactions cannot be classified owing to a lack of insight into the underlying mechanism, whereas in other cases the mechanism is known but does not fall into an existent classification scheme. Examples of such reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome, interstitial nephritis, drug fever, vasculitis, and hepatitis.

The term *desensitization* is classically used to refer to the process of immunologic tolerance to an antigen against which specific IgE antibodies are present. In the case of rapid drug desensitization, progressively increasing doses of the sensitizing drug are administered over the course of several hours to produce a state that allows safe treatment with the medication. Desensitization has also been used to describe drug challenge procedures in which there is no attempt to neutralize drug-specific IgE antibodies. Aspirin desensitization and sulfonamide desensitization (for delayed maculopapular cutaneous reactions in HIV-positive patients) are two such examples. Desensitization does not have a role in treating patients with a history of severe desquamating skin reactions to drugs. Re-administration of the sensitizing drug to such patients is contraindicated because it is dangerous and potentially life threatening.

Graded drug challenge, also called “incremental test dosing,” differs from rapid desensitization in that it does not entail a modification of the immune response to the medication. Graded challenge is a method of cautiously administering a medication to patients who are unlikely to be allergic to it. This procedure is different from desensitization, wherein the patient is known or is assumed to be allergic. The intent of graded challenge is to administer a drug in a

manner so as not to cause a severe reaction. Because the drug is given in piecemeal fashion, if an allergic reaction is provoked, it should be minor and easily treated.

This review discusses desensitization for commonly encountered IgE-mediated and non-IgE-mediated drug allergies. The selection of patients for desensitization and the situations in which desensitization are clinically indicated are reviewed. When known, the mechanism of desensitization is discussed. A discussion of aspirin desensitization (for respiratory-related aspirin sensitivity) is not included, because this topic is covered in detail elsewhere in this issue.

Penicillin desensitization

Patient evaluation and selection

Penicillin allergy is the most commonly reported medication allergy. Approximately 10% of patients report being penicillin allergic, but large-scale studies have shown that at least 80% of these individuals are falsely labeled as allergic and can tolerate treatment with penicillin [4–6]. The large body of research on immediate-type penicillin allergy stems from the availability of validated diagnostic skin testing. Skin test reagents were developed after the immunochemistry of penicillin was elucidated in the 1960s [7,8]. Under physiologic conditions, penicillin spontaneously degrades to reactive intermediates that act as haptens and covalently bind to self-proteins, possibly eliciting an immune response. Approximately 95% of penicillin degrades to the penicilloyl moiety, which is called the major antigenic determinant (Fig. 1). The remaining portion of penicillin degrades to several derivatives (minor antigenic determinants), the most important of which are penicilloate and penilloate (Fig. 1). The commonly used penicillin skin test reagents are listed in Table 2.

Penicillin skin testing should guide the approach to patients with a history of penicillin allergy. Skin test–negative patients may safely receive penicillin, because the negative predictive value of skin testing (using both major and minor determinants) approaches 100% [4–6,9]. Penicillin skin test–positive patients should avoid all penicillin class compounds unless repeat testing subsequently shows them to have lost their sensitivity. Desensitization to penicillin should be considered only when treatment with an alternate class of antibiotics cannot be substituted. For example, the treatment of syphilis during pregnancy requires penicillin, because alternate antibiotics such as erythromycin and clindamycin have inferior cure rates and may not cross the placenta in sufficient quantities. Similarly, if a serious bacterial infection is only sensitive to a penicillin class antibiotic, or if the patient has already failed treatment with an alternate antibiotic, the risk of desensitization is outweighed by the risk of an improperly treated infection.

Because not all of the minor determinants are commercially available in the United States, some practitioners may need to resort to skin testing with Pre-Pen

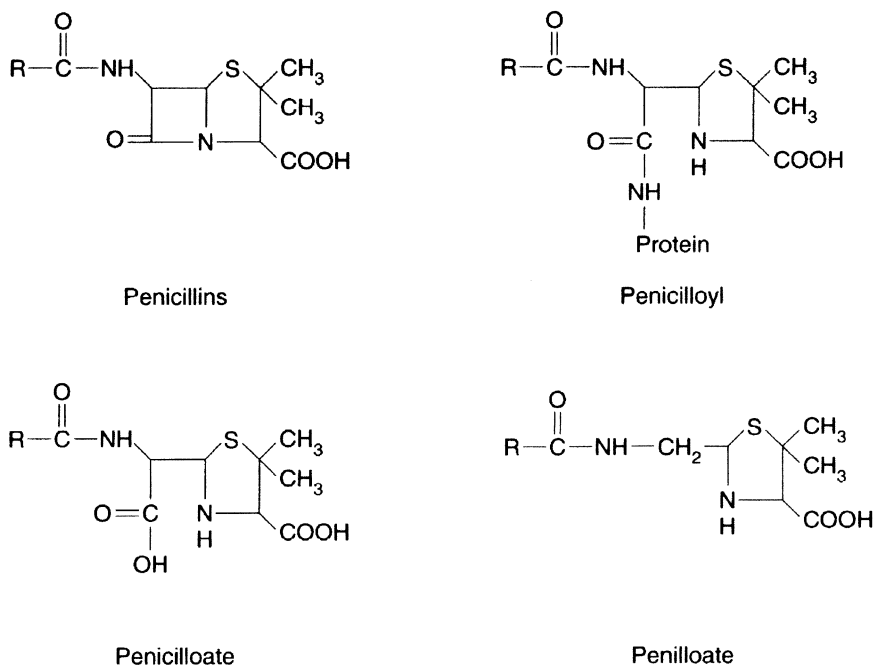


Fig. 1. Structures of the major and minor penicillin antigenic determinants.

and penicillin G. Testing without all of the minor determinants may decrease the sensitivity by 1% to 2%. This value is derived from the fact that only 10% of “all comers” with a history of penicillin allergy have IgE antibodies, and about 10% to 20% of these individuals selectively react to penicilloate or penilloate [4,6]. Because testing with Pre-Pen and penicillin G misses relatively few patients, the consensus opinion is that, if these tests are negative, desensitization generally does not need to be performed [10]. Instead, the drug hypersensitivity practice parameter recommends that such patients receive penicillin by graded challenge, with an initial 1/100 test dose followed by the full therapeutic dose (if no reaction occurred during a brief observation period) [10]. If an allergic reaction develops during the graded challenge, penicillin should only be administered via rapid desensitization.

Table 2

Commonly used penicillin skin test reagents

Reagent	Concentration
Penicilloyl-polylysine (Pre-Pen)	6×10^{-5} M
Penicillin G	10,000 U/mL
Penicilloate	0.01 M
Penilloate	0.01 M
Ampicillin/amoxicillin	1–20 mg/mL

Rapid penicillin desensitization is intended for patients who have evidence of (or are strongly suspected to have) penicillin-specific IgE antibodies. Desensitization does not prevent non-IgE-mediated allergic reactions, as evidenced by reports of serum sickness–like reactions and hemolytic anemia in patients who were successfully desensitized [11,12]. Patients with a history of severe penicillin-induced cutaneous reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, should not receive the drug under any circumstances owing to the risk of inducing a progressive, potentially life-threatening reaction.

Desensitization procedure

Cases of penicillin desensitization accomplished by the administration of gradually increasing doses of penicillin have been reported since the 1940s [13–18]. Most of these reports involved parenteral administration of the medication, and many were associated with significant allergic reactions during or soon after the procedure. More recently, Sullivan and colleagues have established a relatively safer form of penicillin desensitization (Table 3) [19–21]. In this procedure, the starting dose is determined by the amount of penicillin tolerated during skin testing, which usually translates to approximately 1/10,000 of the therapeutic dose. Doubling doses are administered every

Table 3
Penicillin oral desensitization protocol

Step ^a	Penicillin (mg/mL)	Amount (mL)	Dose (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0
Observe patient for 30 minutes, then give full therapeutic dose by the desired route.				

^a Interval between doses is 15 minutes.

From Sullivan TJ. Drug allergy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. *Allergy: principles and practice*. 4th edition. St. Louis: Mosby; 1993. p. 1726–46; with permission.

15 minutes until the full dose is reached. Mild systemic reactions occur in about one third of patients, but no fatal or life-threatening reactions have been reported [19–21]. Mild allergic reactions should be treated; if they do not progress, the dose of penicillin may be advanced. At the completion of oral desensitization, the therapeutic dose of penicillin may be administered via the desired route. For example, pregnant patients treated for syphilis may safely receive intramuscular benzathine penicillin G following oral desensitization with penicillin VK [21,22]. To maintain the desensitized state, the patient requires continual penicillin treatment. Unless a long-acting preparation (such as benzathine penicillin G) is used, this typically translates to oral penicillin taken on a twice-daily basis. If penicillin is discontinued for more than 48 hours, the patient is again at risk for anaphylaxis, and desensitization should be repeated.

Penicillin desensitization can be accomplished in analogous fashion via the intravenous route [12,23]. Two representative intravenous regimens are shown in Tables 4 and 5. The advantages of oral versus intravenous desensitization include lower cost and increased safety. The costs of both regimens were compared at a single medical center. The oral route was found to be approximately half as expensive as the intravenous route [22]. Although there are no randomized trials

Table 4

Penicillin intravenous desensitization protocol with drug added by piggyback infusion

Step ^a	Penicillin (mg/mL)	Amount (mL)	Dose (mg)	Cumulative dose (mg)
1	0.1	0.1	0.01	0.01
2	0.1	0.2	0.02	0.03
3	0.1	0.4	0.04	0.07
4	0.1	0.8	0.08	0.15
5	0.1	1.6	0.16	0.31
6	1.0	0.32	0.32	0.63
7	1.0	0.64	0.64	1.27
8	1.0	1.2	1.2	2.47
9	10.0	0.24	2.4	4.87
10	10.0	0.48	4.8	10.0
11	10.0	1.0	10.0	20.0
12	10.0	2.0	20.0	40.0
13	100.0	0.4	40.0	80.0
14	100.0	0.8	80.0	160.0
15	100.0	1.6	160.0	320.0
16	1000.0	0.32	320.0	640.0
17	1000.0	0.64	640.0	1280.0
Observe patient for 30 minutes, then give full therapeutic dose by the desired route.				

^a Interval between doses is 15 minutes.

From Sullivan TJ. Drug allergy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. *Allergy: principles and practice*. 4th edition. St. Louis: Mosby; 1993. p. 1726–46; with permission.

Table 5

Penicillin intravenous desensitization protocol using a continuous infusion pump

Step ^a	Penicillin (mg/mL)	Flow rate (mL/h)	Dose (mg)	Cumulative dose (mg)
1	0.01	6	0.015	0.015
2	0.01	12	0.03	0.045
3	0.01	24	0.06	0.105
4	0.1	5	0.125	0.23
5	0.1	10	0.25	0.48
6	0.1	20	0.5	1.0
7	0.1	40	1.0	2.0
8	0.1	80	2.0	4.0
9	0.1	160	4.0	8.0
10	10.0	3	7.5	15.0
11	10.0	6	15.0	30.0
12	10.0	12	30.0	60.0
13	10.0	25	62.5	123.0
14	10.0	50	125.0	250.0
15	10.0	100	250.0	500.0
16	10.0	200	500.0	1000.0
Observe patient for 30 minutes, then give full therapeutic dose by the desired route.				

^a Interval between doses is 15 minutes.

comparing the safety of oral and intravenous penicillin desensitization, the oral route would seem to be safer. Based on epidemiologic data dating back to the 1950s, it is known that oral penicillin induces fewer allergic reactions than penicillin administered parenterally [20,24]. Only six deaths have been reported secondary to immediate-type reactions to oral penicillin, whereas parenteral administration has resulted in thousands [20]. Sullivan et al also hypothesized that oral desensitization is safer because it is less likely to expose patients to multivalent penicillin conjugates and polymers, which are thought to have an important role in IgE-mediated allergic reactions [20].

Penicillin desensitization should be performed by physicians who are familiar with the procedure and with the treatment of anaphylaxis. The physician should remain present throughout the entire procedure. Patients should have intravenous access, with medications and equipment to treat allergic reactions in close vicinity. Because penicillin desensitization has proved to be relatively safe, it is reasonable to perform the procedure in a general ward or outpatient setting as opposed to an intensive care unit. Patients should be observed continually for the presence of IgE-mediated allergic symptoms, along with regular monitoring of vital signs and peak expiratory flow values. Before the procedure, patients with asthma or other pulmonary disease should be controlled optimally. Treatment with beta-adrenergic blocking medications must be discontinued before desensitization. Pretreatment with systemic corticosteroids and antihistamines is contra-

indicated, because these medications do not prevent IgE-mediated anaphylaxis and may mask early signs of an allergic reaction.

Mechanism

Several investigators have shown that skin test responses to penicillin determinants diminish or become negative in a majority of patients following penicillin desensitization [11,19,25], proving that penicillin desensitization renders mast cells unresponsive (or less responsive) to the relevant penicillin allergenic determinants. Sullivan also demonstrated that skin test responses to aeroallergens, histamine, and compound 48/80 (a chemical inducer of mast cell degranulation) were unaffected by penicillin desensitization [11]. These results indicate that penicillin desensitization is antigen specific, does not impair mast cells' ability to respond to nonpenicillin IgE signals, and does not cause a generalized depletion of mast cell mediators or tachyphylaxis to the effects of these mediators.

The precise immunologic mechanism responsible for penicillin desensitization remains unknown. One theory is that gradual introduction of penicillin molecules causes cross-linking of penicillin-specific IgE on the surface of mast cells to occur in gradual fashion, keeping the intracellular signal (which would normally cause degranulation) below a clinical threshold. Another possible explanation is that univalent penicillin-carrier protein molecules prevent cross-linking of surface IgE and the transmission of an intracellular signal.

Rapid desensitization to nonpenicillin antibiotics

Evaluation and patient selection

Unlike for penicillin, the immunochemistry of other classes of antibiotics is unknown. Other antibiotics differ from penicillin in that they are chemically inert and must undergo metabolism (bioactivation) to reactive intermediates to bind to host proteins. Unfortunately, with few exceptions, the identity of the immunogenic determinants produced by metabolism is not known. This lack of insight has prevented the development of validated diagnostic skin test reagents for drug-specific IgE antibodies directed against nonpenicillin antibiotics. Consequently, it is more difficult for clinicians to determine which patients have immediate-type allergies and may require rapid desensitization.

Skin testing with native antibiotics can yield some useful information. If a concentration that is nonirritating in control subjects is used, a positive response strongly suggests the presence of drug-specific IgE antibodies [10]. Nevertheless, a negative response does not rule out immediate-type allergy, because such testing may not include all relevant allergenic determinants. Nonirritating concentrations of many antibiotics can be found in published case reports. A useful reference is the study by Empedrad et al [26] that systematically determined

Table 6

Nonirritating intradermal skin test concentrations of selected intravenous antibiotics

Antibiotic	Full-strength concentration (mg/mL)	Nonirritating concentration (dilution from full-strength)
Cefotaxime	100	10-fold
Cefuroxime	100	10
Cefazolin	330	10
Ceftazidime	100	10
Ceftriaxone	100	10
Tobramycin	40	10
Ticarcillin	200	10
Clindamycin	150	10
Gentamycin	40	10
Trimethoprim-sulfa	80 (sulfa component)	100-fold
Levofloxacin	25	1000-fold
Erythromycin	50	1000
Nafcillin	250	10,000-fold
Vancomycin	50	10,000
Azithromycin	100	10,000

From Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol* 2003;112:629–30; with permission.

nonirritating concentrations of 15 commonly used antibiotics in 25 nonallergic individuals (Table 6).

As is true for penicillin, rapid desensitization with other antibiotics should be considered only for patients with IgE-mediated allergies and only when an alternative non-cross-reacting antibiotic cannot be substituted. Determination of whether re-administration of an antibiotic requires desensitization should be based on the reaction history and skin testing with a nonirritating concentration of the antibiotic. Patients with a convincing or recent immediate-type allergic

Table 7

Example of graded challenge with oral trimethoprim-sulfamethoxazole (TMP-SMX) in a patient with a distant mild immediate-type allergic reaction

Step ^a	TMP-SMX (mg/mL)	Amount (mL)	Dose (mg)
1	4	0.25	1
2	4	1.0	4
3	40	0.5	20
4	40	2.0	80
5	NA	1 tablet	400

Abbreviation: NA, not applicable.

^a Interval between doses is 30 minutes. Dose is expressed as sulfamethaxazole portion of TMP-SMX. If an allergic reaction occurs, formal desensitization should be performed.

reaction to a given antibiotic should receive the medication via desensitization. Likewise, a positive skin test response with a nonirritating concentration of the antibiotic is a clear indication for desensitization. For patients who test negative, the antibiotic should be administered via desensitization or graded challenge, depending on the severity and time elapsed since the previous allergic reaction. If a patient reports a pruritic rash (with no other symptoms) during the first day of a course with a sulfonamide antibiotic 20 years ago, it would be reasonable to reintroduce the medication via graded challenge (Table 7). Conversely, a patient with a recent allergic reaction or a history of anaphylaxis should undergo desensitization. If the practitioner is uncertain about the severity or type of the previous reaction, desensitization should be performed. Skin testing with the native antibiotic is also useful, because the amount of drug tolerated during testing can serve as the starting point for desensitization.

Desensitization procedure

The principles learned from penicillin desensitization can be applied to other antibiotics to which patients have IgE-mediated allergies. Following Sullivan's penicillin desensitization publications [19–21], successful acute desensitization has been reported with virtually all classes of antibiotics, including cephalosporins, monobactams, carbapenems, aminoglycosides, sulfonamides, vancomycin, quinolones, and macrolides [27–36]. The desensitization protocol generally parallels that of penicillin desensitization, with progressively increasing doses of the antibiotic administered in frequent time intervals. In place of

Table 8
Ciprofloxacin oral desensitization protocol

Step ^a	Ciprofloxacin (mg/mL)	Amount (mL)	Dose (mg)	Cumulative dose (mg)
1	0.1	0.5	0.05	0.05
2	0.1	1.0	0.1	0.15
3	0.1	2.0	0.2	0.35
4	0.1	4.0	0.4	0.75
5	0.1	8.0	0.8	1.55
6	1.0	1.6	1.6	3.15
7	1.0	3.2	3.2	6.35
8	1.0	6.4	6.4	12.75
9	1.0	12.8	12.8	25.55
10	10.0	2.5	25.0	50.55
11	10.0	5.0	50.0	100.55
12	10.0	10.0	100.0	200.55
13	NA	1 tablet	250.0	450.55

Abbreviation: NA, not applicable.

^a Interval between doses is 15 minutes.

From Lantner RR. Ciprofloxacin desensitization in a patient with cystic fibrosis. *J Allergy Clin Immunol* 1995;95:1001–2; with permission.

Table 9

Ceftriaxone intravenous desensitization protocol using a continuous infusion pump

Step ^a	Ceftriaxone (mg/mL)	Flow rate (mL/h)	Dose (mg)	Cumulative dose (mg)
1	0.01	6	0.015	0.015
2	0.01	12	0.03	0.045
3	0.01	24	0.06	0.105
4	0.1	5	0.125	0.23
5	0.1	10	0.25	0.48
6	0.1	20	0.5	1.0
7	0.1	40	1.0	2.0
8	0.1	80	2.0	4.0
9	0.1	160	4.0	8.0
10	10.0	3	7.5	15.0
11	10.0	6	15.0	30.0
12	10.0	12	30.0	60.0
13	10.0	25	62.5	123.0
14	10.0	50	125.0	250.0
15	100.0	10	250.0	500.0
16	100.0	20	500.0	1000.0
17	100.0	40	1000.0	2000.0

^a Interval between doses is 15 minutes.

bolus intravenous dosing, some investigators have used a continuous infusion of the antibiotic with incremental increases in the infusion rate [32,36]. Representative examples of oral and intravenous desensitization protocols are shown in Tables 8 and 9. If a given antibiotic is available in oral and intravenous forms, oral desensitization is preferred over the intravenous route for the reasons discussed earlier.

The precautions reviewed for penicillin desensitization similarly apply to carrying out the procedure with other classes of antibiotics. Desensitization should only be performed by physicians familiar with the procedure and in a medical setting with intravenous access and preparedness to treat allergic reactions. Patients should be observed continually, and a physician should remain in attendance throughout the procedure. Patients with underlying lung disease should be controlled optimally before desensitization. As is true for penicillin, to maintain the desensitized state, the antibiotic must be administered regularly (the frequency being dependent on the drug's half-life).

Mechanism

The underlying immunologic mechanism for desensitization with nonpenicillins is probably the same as for penicillin desensitization. As is true for penicillin, desensitization seems to render mast cells less unresponsive to the sensitizing antibiotic. Anne et al [37] and Lin [38] independently demonstrated a loss of skin test reactivity to vancomycin following successful desensitization. Presumably, desensitization with nonpenicillins is also antigen specific and does not

diminish the mast cells' ability to react to other allergens, but this has not been investigated.

Sulfonamide desensitization of HIV-positive patients

Patient evaluation and selection

Patients who are infected with HIV are at greatly increased risk of experiencing cutaneous reactions to a variety of medications [39,40], particularly sulfonamide antibiotics. The incidence of skin rashes owing to trimethoprim-sulfamethoxazole (TMP-SMX) in HIV-positive patients is 40% to 80% [41–43] compared with a 3.3% reaction rate in normal individuals [44]. The typical TMP-SMX–induced reaction in HIV-positive patients occurs during the second week of treatment and consists of a generalized maculopapular eruption that is usually accompanied by fever and pruritus. The underlying mechanism responsible for these reactions is unknown and is not due to drug-specific IgE or IgG antibodies [41].

TMP-SMX is the drug of choice to treat a variety of HIV-associated infections. Most notably, it is the recommended first-line antibiotic for the prophylaxis and treatment of *Pneumocystis carinii* pneumonia (PCP) [45]. Consequently, physicians commonly encounter patients with HIV who have previously reacted to TMP-SMX and yet require treatment with the antibiotic. These patients should be considered for desensitization with TMP-SMX. Because there is no diagnostic test to confirm whether a patient is at risk of reacting to TMP-SMX, the selection of patients for the procedure is made based on the reaction history. Only patients with a history of the typical delayed maculopapular reaction should be desensitized. Patients with a previous reaction consistent with an IgE-mediated mechanism should undergo rapid desensitization (as described in the previous section) rather than the procedure discussed in the next section. Sulfonamides may cause a variety of other allergic reactions, such as serum sickness–like reactions, vasculitis, hypersensitivity syndrome, pneumonitis, interstitial nephritis, immune-mediated hematologic disorders, drug fever, Stevens-Johnson syndrome, toxic epidermal necrolysis, and others. Patients who have experienced one of these reactions are not candidates for desensitization.

Desensitization procedure

Although the term *desensitization* classically describes procedures in which specific IgE antibodies are neutralized, its meaning has been extended for procedures such as TMP-SMX desensitization in patients with HIV. There are numerous citations of various TMP-SMX desensitization procedures in the literature [46–56]. Most of these publications describe small groups of patients, and virtually each one used a unique protocol. A representative sample of TMP-SMX desensitization protocols is shown in Table 10. The study designs differed in terms of the starting dose, the incremental increase between doses, the time

Table 10
Representative sample of published TMP-SMX desensitization protocols

Study	Number of patients	Initial dose	Number of steps	Total duration	Success rate (%)
Absar et al [46]	27	2 mg	10	10 d	85
Gluckstein and Ruskin [47]	21	0.02 mg	5	5 h	71
Nguyen et al [48] ^a	45	10 ng	40	36 h	60
Belchi-Hernandez et al [49]	34	1 mg	21	11 d	79
Kalanadhabhatta et al [50]	13	20 ng	37	27 h	100
Caumes et al [51]	48	4 mg	8	3 d	77
Rich et al [52]	22	20 ng	24	8 d	86
Ryan et al [53]	14	2 mg	33	33 d	69
Demoly et al [54]	44	1 µg	12	6 h	95
Bonfanti et al [55] ^a	34	10 ng	40	36 h	79
Yoshizawa et al [56]	17	2 mg	10	5 d	88

^a Indicates identical protocols; dose is expressed as sulfamethoxazole portion of TMP-SMX.

interval between doses, and the total duration of the procedure. In addition, only some patients were pretreated with antihistamines or corticosteroids. The investigators' approach to treating reactions during desensitization also differed. Some chose to "treat through" and add anti-allergy medications, whereas others aborted the procedure. Desensitizations were performed in inpatient settings, outpatient settings, or completed by patients at home after hospital discharge. In most cases, patients received TMP-SMX orally rather than intravenously. The desensitizations were generally described as safe, and the reactions during or after the procedure were minor and easily treated. Nevertheless, the reports are not completely free of serious reactions, with rare occurrences of anaphylaxis, toxic epidermal necrolysis, and hypotension with myocardial infarction [51,57,58]. Unfortunately, no attempt has been made to standardize TMP-SMX desensitization protocols.

The lack of a diagnostic test for TMP-SMX hypersensitivity in HIV-positive patients makes critical analysis of desensitizations difficult. Some patients with previous reactions to TMP-SMX are able to tolerate re-administration of the drug, presumably owing to a loss of their sensitivity [59]. Patients with more recent reaction histories are more likely to fail desensitization than are patients who have distant reaction histories [60]. These observations suggest that, among a typical group of patients who undergo TMP-SMX desensitization, some individuals are not truly allergic.

Only one study has directly compared the efficacy of TMP-SMX desensitization and simple re-administration [55]. In a multicenter trial, Bonfanti and colleagues randomized HIV-positive patients with documented TMP-SMX reactions to receive the antibiotic via desensitization (via a 2-day, 40-dose protocol) or re-challenge (single dose). The success rates were 79% and 72% in the desensitization and re-challenge groups, respectively, and the difference was not statistically significant. The results of the Bonfanti trial place into question the

validity of other “uncontrolled” TMP-SMX desensitization studies, which likely included many patients who were not truly at risk of reacting to TMP-SMX at the time of desensitization. The inclusion of varying numbers of nonallergic patients may also partly explain the disparate desensitization success rates (Table 10), particularly because most studies included relatively few patients and would be susceptible to such a variable.

For clinical practice, the available data do not allow the selection of any single TMP-SMX desensitization protocol as most effective. Comparative trials of different protocols are lacking and are sorely needed. Indirect comparison is difficult owing to the multitude of variables present among the studies. The success rates of many dissimilar protocols are comparable, and there are no apparent differences in safety. Because predictors of success and failure are not consistent, it is not possible to “tailor” a particular protocol for a specific type of patient. For instance, some researchers have found that low CD4+ counts are predictive of successful desensitization [51,59], whereas others have found no such correlation [48,55]. It appears that clinicians may employ a number of different TMP-SMX desensitization protocols with similar hopes for success and safety.

Mechanism

Because the pathogenesis of TMP-SMX–induced reactions in HIV-positive patients is unclear, understanding of the mechanism of desensitization is also limited. Sulfonamide antibiotics are metabolized in the liver by N-acetylation to yield nontoxic metabolites that are excreted (Fig. 2). Alternatively, sulfonamides may undergo N-oxidation catalyzed by cytochrome P450 enzymes to form reactive hydroxylamines, which can be further auto-oxidized to reactive nitroso-

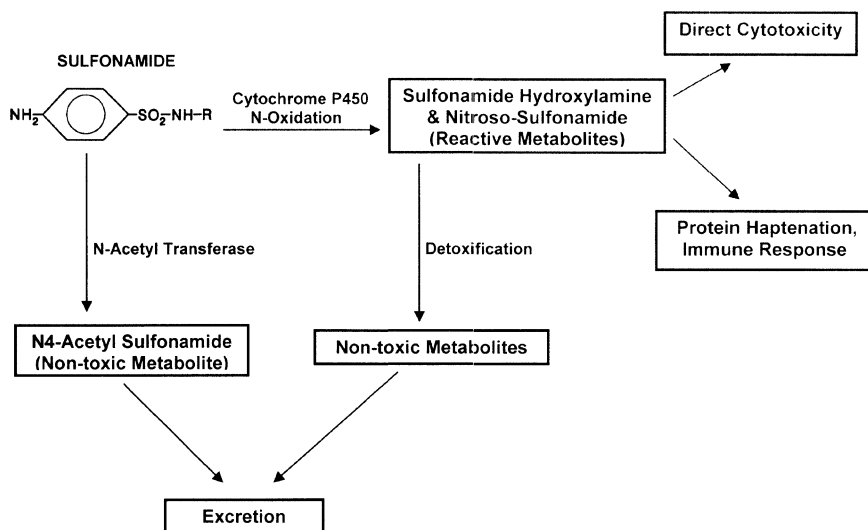


Fig. 2. Sulfonamide metabolic pathways.

species. Reactive metabolites can cause direct cytotoxicity or act as haptens, binding to host proteins and leading to the production of an immune response. Reactive intermediates are normally detoxified by glutathione or other scavengers via a reduction reaction. In addition to metabolism in the liver, formation of reactive metabolites can take place in monocytes and neutrophils via the myeloperoxidase pathway.

Evidence suggests that direct toxicity and immune effects contribute to the pathogenesis of various sulfonamide adverse reactions [41]. Regardless of the final pathway of damage, the aromatic amine group at the N4 position is critical for the development of most sulfonamide adverse reactions. Among the sulfonamides, only the antibacterial agents contain an aromatic amine group at the N4 position. Because other sulfonamides, such as oral hypoglycemic drugs, diuretics, and celecoxib, lack an aromatic amine at the N4 position, they are likely to be tolerated by patients with sulfonamide antibiotic allergies; however, clinical proof for this lack of cross-reactivity is limited [41,60–62].

The propensity of HIV-positive patients to react to TMP-SMX and other sulfonamides is probably caused by several factors. There are limited data to support each of several theories [41,60,63,64], but it is not clear how desensitization may modify them to allow safe administration of the drug. First, HIV-positive patients may be “slow” acetylators and may shunt more of the parent sulfonamide toward the oxidative cytochrome P450 pathway with subsequent formation of reactive metabolites (Fig. 2). Second, a relative deficiency of glutathione or other scavengers (which detoxify reactive intermediates) would also result in an excess of hydroxylamine and nitroso-metabolites. Third, HIV infection or infection with opportunistic organisms may stimulate the activity of cytochrome P450 enzymes and lead to an increased rate of oxidation and production of reactive metabolites. Lastly, viral infections stimulate production of interferon- γ , which causes increased expression of major histocompatibility complex (MHC) class I and class II cell surface molecules, including on keratinocytes. This condition would favor the presentation of processed drug antigens on MHC molecules to drug-specific CD4+ and CD8+ T cells, resulting in delayed skin eruptions.

Summary

Drug allergy is commonly encountered in clinical medicine. Fortunately, when properly evaluated, most patients are found to not be truly allergic and may receive the medication in question. Patients who are confirmed to be allergic and who require treatment with the implicated drug may be candidates for desensitization. Rapid desensitization for IgE-mediated drug hypersensitivity was first described with penicillin. It involves the administration of doubling doses of penicillin until the full therapeutic dose is reached. Patients with IgE-mediated allergies to other antibiotic classes have also been desensitized successfully via protocols patterned on penicillin desensitization. HIV-positive patients are at

particularly high risk of experiencing delayed cutaneous reactions to TMP-SMX, and they frequently require treatment with this antibiotic. Although the mechanism of this reaction is not well understood and does not involve IgE antibodies, “desensitization” protocols have been described that allow these patients to tolerate the antibiotic. Except for the typical delayed TMP-SMX reactions in HIV-positive patients, other non-IgE-mediated reactions to antibiotics (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or interstitial nephritis) are not amenable to desensitization.

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