

DRUG CHALLENGE AND DESENSITIZATION PROTOCOLS

Paul A. Greenberger, MD

Drug challenges and desensitization protocols can be of great value to patients who require medications that have previously caused allergic reactions. In the case of penicillin or cephalosporin allergy, it is possible to identify patients at high risk of an immediate hypersensitivity reaction because of the presence of anti-penicillin IgE antibodies that are directed to the β -lactam ring structure.^{26, 30} Conversely, if IgE antibodies to penicillin major and minor determinants are absent, the incidence of an immediate hypersensitivity reaction on administration of β -lactam antibiotics approaches 1% or less.³⁰ Desensitization protocols can be separated into true immunologic desensitization, in which IgE antibodies are bound to the medication, and test-dosing regimens, in which risk of a repeated allergic reaction is high, but no in vitro or in vivo tests are available to verify or monitor the presumed immunologic sensitivity.²⁶ In the case of radiographic contrast material idiosyncrasy, pretreatment medications combined with the use of lower osmolality radiographic contrast media have helped to reduce the risk of repeated immediate generalized reactions.¹⁹

ISSUES SURROUNDING DRUG CHALLENGE AND DESENSITIZATION PROTOCOLS

The apparent risk of a current allergic or immunologic-in-type reaction should be assessed, and the essentiality of the medication must be verified (Table 1). Ideally, the physician administering the incriminated medication should not be the physician who confirmed the indication for the medication or diagnostic agent. An assessment of the patient should include the overall status (e.g., is the patient receiving mechanical ventilation?), the seriousness of the condition that requires administration of a potentially dangerous agent, the likelihood of the

From the Division of Allergy-Immunology, Department of Medicine, and the Ernest S. Bazley Asthma and Allergic Diseases Center of Northwestern Memorial Hospital and Northwestern University Medical School, Chicago, Illinois

Table 1. ISSUES SURROUNDING DRUG CHALLENGE AND DESENSITIZATION PROTOCOLS

Risk of the patient experiencing a current adverse reaction
High
90%–95% (penicillin-induced anaphylaxis 1 year ago; penicillin indicated now) ³¹
60%–90% (cross-reactions among NSAIDs in an aspirin-intolerant patient) ²³
Medium
25%–30% (penicillin-induced anaphylaxis 10 years ago; penicillin indicated now) ³¹
Low
5.4%–16.5% (first generation cephalosporin use in a penicillin-allergic patient) ²⁷
10% (second generation cephalosporin use in a penicillin-allergic patient) ⁷
Very Low
2% (third generation cephalosporin use in a penicillin-allergic patient) ³
1% (penicillin-induced anaphylaxis 1 year previously with no current immediate cutaneous reactivity to reactive penicillin major and minor determinants; penicillin indicated now) ³⁰
Essentiality of the medication or diagnostic agent
Benefit to the patient from therapeutic readministration
Patient factors
Overall status
Fluctuating blood pressure or sensorium
Cardiovascular reserve
Bacteremic or septic
<i>Pneumocystis carinii</i> pneumonia
Psychological status
Appropriate concern
Excessive fear
Hospital readiness
Physician knowledge and expertise with challenges and desensitization protocols
Physician colleagues
Steroid-phobia should a generalized cutaneous eruption occur
Overestimation of benefit to patient from readministration of incriminated medication

patient's surviving an episode of hypotension during a controlled challenge, the benefit from administration of incriminated medications or diagnostic agents, and the level of anxiety that may be present. The latter may be justified or a manifestation of fear about the subsequent treatment or surgery might result from receiving the incriminated agent. One example is the patient who fears coronary artery bypass grafting surgery and overemphasizes a previous radiocontrast material reaction in an attempt to avoid undergoing coronary angiography with surgery to follow.

Will the referring physician interfere with treatment of an allergic drug reaction that occurs during administration of an incriminated medication? An example is the patient with *Pseudomonas aeruginosa* bacteremia who is postoperative and requires meropenem but is known to have developed an erythematous, exfoliative eruption after 3 days of piperacillin and ciprofloxacin. The patient is found to be skin test negative to major and minor penicillin determinants, essentially excluding an immediate allergic reaction to β -lactam drugs.³⁰ A delayed cutaneous reaction, however, will not be excluded by the absence of immediate cutaneous reactivity to penicillin determinants. If the referring physician refuses to allow systemic corticosteroids to be administered and if the related penicillin (meropenem) causes an exfoliative, erythematous rash, the drug challenge should not be carried out.

PRINCIPLES OF DRUG CHALLENGE AND DESENSITIZATION

Drug challenge refers to readministration of incriminated medications to patients assumed to be at increased risk of allergic or other adverse reaction.²⁶ In some cases, the risk of a current anaphylactic reaction is low as in the penicillin-allergic patient who has no identifiable antipenicillin IgE antibodies by immediate skin testing.³⁰ A stepwise challenge is performed with monitoring of the patient for untoward outcomes. The pace of the challenge is determined by a number of factors including (1) the indication, (2) the severity of the previous adverse reaction, (3) the duration of time between the previous administration of the incriminated medication and the onset of allergic reaction, (4) the overall status of the patient and ability to withstand a severe allergic reaction, (5) the location of the patient (e.g., ambulatory, inpatient, intensive care unit), (6) the likelihood of the incriminated medication or agent to cause the reported reaction, (7) medical literature, (8) the patient's level of acceptance of the challenge, and (9) physician experience with challenges.

Desensitization protocols can be categorized as either true immunologic desensitization or test-dosing protocols, in which the patient risk is assumed to be high, but no *in vivo* or *in vitro* test is available to demonstrate immunologic sensitivity or reactivity.²⁶ During readministration of the incriminated medication in either circumstance, an adverse reaction may occur and be harmful to the patient. It is hoped that the desensitization protocol will be carried out so that the current adverse reaction will not become life-threatening because this defeats the purpose of desensitization protocols. In the case of patients who have experienced anaphylaxis to a mandatory medication, the desensitization protocol might be considered an example of controlled anaphylaxis. In other cases in which the risk of a current allergic reaction is low, the readministration of incriminated medications can be carried out with step-wise test-dosing challenges.

True Immunologic Desensitization

When the mechanism of the allergic reaction has been anaphylactic, implying presence of IgE antibodies activating mast cells, true desensitization implies disappearance of skin and serum anti-medication IgE antibodies.¹⁶ For example, a patient had developed a generalized morbilliform (maculopapular) eruption after 3 days of penicillin G administration for *Serratia marcescens* empyema and bacteremia. Several attempts at eradication of the *Serratia* with cephalosporins were unsuccessful and had not caused any allergic reactions as well. The patient was skin tested and found to demonstrate immediate cutaneous reactivity to a penicillin minor determinant mixture (with reactivity to benzylpenicilloate) and a specially prepared minor determinate of carbenicillin, α -carboxybenzylpenicilloate (10^{-3} M). There were no immediate cutaneous reactions to the major penicillin determinant, benzylpenicilloyl-polylysine (BPL), penicillin G, and carbenicillin. Intravenous carbenicillin was administered initially with 0.05 mg given as 0.1 mL of a solution containing 0.5 mg/mL of carbenicillin. Such a dose should be subanaphylactic. When doubling doses were administered every 15 minutes and the 11th dose at 51.2 mg (total cumulative dosage = 102.35 mg), generalized flushing occurred that lasted 2 hours. The patient was skin tested and was nonreactive to the α -carboxybenzylpenicilloate with a positive histamine control. Carbenicillin was restarted, and the flush lasted another 1.5 hours with increase in the pulse from 82 to 115 beats per

minute. The patient was able to receive for 4 days 30 g per day of intravenous carbenicillin without additional flushing or evidence of an allergic reaction. The patient died unexpectedly and had subacute bacterial endocarditis and metastatic carcinoma of the cervical spine. Subsequently, it was demonstrated that the serum could passively transfer the anti-penicilloate IgE antibodies and the Prausnitz-Küstner titers were 1:30 prior to desensitization and 1:3 at the time of the initial flushing from carbenicillin. An additional sample of serum obtained during true desensitization could not passively transfer any anti-penicilloate sensitivity.¹⁶ This case demonstrates that such desensitization implies loss of passive transfer (Prausnitz-Küstner) reactivity and immediate cutaneous reactivity. In addition, in the process of desensitization, it is likely that the patient will experience some manifestations of drug hypersensitivity. Indeed, in this case, a cumulative dose of 102 mg was sufficient to induce the carbenicillin allergic reaction, and emphasizes some of the issues listed in Table 1. For example, how mandatory is the readministration of the medication and what is the ultimate impact on the patient?

Test-Dosing Protocols

Test-dosing protocols refer to readministration of incriminated medications in which the risk of allergic reaction ranges from high to low but in which *in vitro* and *in vivo* tests are not available to verify the risk status or guide readministration of the medication in question.²⁶ The principal method is to begin the test-dosing protocol with a dose less than a reactive dose so that if the adverse reaction occurs, the physician is not faced with an uncontrollable situation. Alternatively, if the risk of reaction is extremely low or nil, such as that which occurs with local anesthetic allergy, the initial dose is purposely less than a therapeutic dose in case the patient experiences an acute hyperventilation reaction or vasovagal reaction.²⁶ During rapid test-dosing protocols, the patient is examined before the next dose of medication is administered so that the onset of symptoms can be documented and assessed. In the setting of sulfonamide test-dosing in patients with inflammatory bowel disease^{8, 29} or in patients with AIDS,^{5, 8, 11, 12, 14, 15, 18, 20, 32} there is a high likelihood of reproducing an allergic or adverse reaction during readministration of the incriminated medication. When the indication is not urgent, such as occurs in inflammatory bowel disease, a slow desensitization protocol has been suggested that involves some 32 days for testing.²⁹ Alternatively, more rapid approaches have been suggested, such as starting with a dose of 0.01 of the therapeutic dose and increasing to 0.1 of the dose on the following day.²⁶ If no adverse reaction has occurred by the third day, 0.5 of the dose is administered. Finally, on the following day, the full dose is administered. If the patient develops an erythematous rash that resembles drug hypersensitivity, the indication for the medication is re-evaluated. If the patient agrees and the medication is essential, the next dose is reduced to perhaps 0.33 to 0.5 of the reactive dose. Hopefully, the patient can then receive the necessary medication with a slower progression of dosage; however, the erythematous rash may reappear. As for patients with AIDS, reasonable alternatives may not exist or will have been tried already. When a generalized morbilliform rash has developed but no mucous membrane, hepatic, or renal involvement has occurred, continuation of the medication will be attempted along with prednisone administration (20–30 mg daily).^{8, 18, 26} A number of successful desensitization procedures have been performed with the patient able to reach the therapeutic dose, and prednisone was discontinued after 2 to 3 weeks.^{8, 18, 26}

Impact of the Previous Adverse Reaction

Desensitization can be dangerous, and previous adverse reactions should not be minimized.²⁶ The interval of time since the previous reaction and the quality of the reaction can influence the decision to proceed with test-dosing and the specific regimen employed. Some examples of adverse drug reactions and the current risk are presented in Table 2. When the previous adverse drug reaction was Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, anaphylactic shock, hepatitis, or a hematologic reaction, test-dosing should be discouraged because the benefit to the patient may not be offset by the risks of readministration of the incriminated medication.^{10, 26} Some desensitization protocols are too dangerous or ill advised to carry out for the safety of the patient and physician. Alternatively, the risk of current immediate hypersensitivity reaction to β -lactam antibiotics can be determined using penicillin major and minor determinants.³⁰ For example, if the patient has experienced a convincing IgE-mediated allergic reaction to penicillin within 1 year of necessary readministration of a β -lactam antibiotic, the likelihood of the patient still having anti-penicillin IgE antibodies is greater than 90%.³¹ Such patients are at high risk of anaphylaxis should they receive β -lactam antibiotics. Alternatively, if the previous convincing allergic reaction to β -lactam antibiotics had occurred more than 10 years previously, the current likelihood that the patient has anti-penicillin IgE antibodies is 20% to 30%.³¹ These data are an example of how patients may be categorized by risk when in vivo tests are available. Regrettably, penicillin minor determinants are not available commercially, and testing with the major determinant, benzylpenicilloyl-polylysine and penicillin G (10,000 units/mL) identifies about 85% to 93% of patients who have antipenicillin IgE antibodies.

The time that elapsed between the administration of the incriminated medication and the onset of the untoward reaction should be considered in planning the desensitization challenge. For example, if a patient with AIDS requires sulfamethoxazole-trimethoprim for prophylaxis or treatment of *Pneumocystis*

Table 2. IMPACT OF PREVIOUS ADVERSE DRUG REACTION ON THE CURRENT CHALLENGE OR DESENSITIZATION

Example	Impact
Piperacillin-induced nonpruritic rash 12 years previously	If penicillin skin tests are not available, cautious test challenge is indicated
Morbilloform rash from sulfamethoxazole-trimethoprim 2 years previously in a patient with AIDS	Cautious test challenge over several days; repeat reaction is likely
Stevens-Johnson syndrome from phenytoin 7 years previously	Very high risk; avoid rechallenge
Zidovudine-induced malaise, fever, and rash	Cautious test challenge over several days
Acute pruritic rash from vancomycin	Reduce infusion rate to over 2-8 hours
Acute angioedema from captopril	Cross-reactivity high; avoid ACE inhibitors
Aspirin- and ibuprofen-induced bronchoconstriction and urticaria	Avoid NSAIDs; try salsalate, trisalicylate, or acetaminophen

ACE = angiotensin converting enzyme.

carinii pneumonia, the challenge should be undertaken with the knowledge that an untoward reaction is likely to occur. If the patient had experienced an erythematous, papular eruption that occurred after 2 weeks of treatment, one approach would be to administer trimethoprim-sulfamethoxazole over 4 days with one dose per day. There is not a significant risk of anaphylaxis compared with a delayed cutaneous reaction occurring after 1 week's administration. Therefore, the first dose could utilize the pediatric suspension (40 mg trimethoprim/200 mg sulfamethoxazole per 5 mL) and be 2.5 mL delivering 20 mg trimethoprim/100 mg sulfamethoxazole. The next day, the patient would receive 5 mL; on the third day, the patient would receive 7.5 mL. If no adverse reaction had occurred, on the fourth day, the patient would receive 1 double-strength tablet containing 160 mg trimethoprim/800 mg sulfamethoxazole. This dose could be continued for 2 days and then increased to 1 tablet twice daily for 2 days. Higher dosages could be used, and the patient should be observed for evidence of drug hypersensitivity or toxicity.

If the history of the trimethoprim-sulfamethoxazole reaction was that of a generalized, pruritic, erythematous rash or urticaria, there is a likelihood of acute urticaria and angioedema or anaphylaxis occurring. Either component could have been responsible for the allergic reaction, and IgE antibodies have been demonstrated to the sulfamethoxazole moiety⁹ or trimethoprim.² The desensitization protocol should be modified to begin with a subanaphylactic dose that can be 0.16 mg trimethoprim/0.8 mg sulfamethoxazole obtained by mixing 1.0 mL of the pediatric suspension with 9.0 mL of water. From this 1:10 dilution, administer 0.2 mL. If there is no reaction in the first 20 minutes, depending on the urgency of the readministration, administer 0.8 mL of this 1:10 dilution next. Then, sequential administration can be with 1 mL followed by 2 mL and 5 mL of the undiluted pediatric suspension. If acute pruritus and urticarial lesions develop, the necessity of the trimethoprim-sulfamethoxazole should be re-established before continuing. If one must continue with the true desensitization, reducing the dose to 2 mL could be tried. If no symptoms or signs occur with 2 mL, then 4 mL and then 5 mL can be administered to desensitize the patient. Alternatively, if no allergic reaction occurs after the dose of 5 mL, then 7.5 mL and 10 mL in adults can be administered. It is preferable to avoid gaps in therapy once the patient has reached maintenance doses. Further, if a late cutaneous reaction occurs, which would be unlikely in the patient whose initial allergic reaction mimicked an IgE-type reaction, physicians should not discontinue the trimethoprim-sulfamethoxazole. Instead, the specialist can reduce the next dose and try to "treat through" to neutralize any antimedication IgE antibodies that are present.

When there is little information about readministration of an essential medication, it is useful to consider the initial adverse reaction and when it emerged during the therapy. For example, a patient with AIDS, toxoplasma encephalitis, and chronic liver disease had developed fever, a maculopapular skin rash, and malaise on the fifth day of zidovudine administration.¹³ The patient received methylprednisolone, 120 mg daily; zidovudine was discontinued. After 15 days, the rash had resolved and zidovudine was considered indicated. The patient was receiving methylprednisolone, 24 mg daily, and this dose was continued through the subsequent readministration of zidovudine. Clearly, the patient had to be considered at high risk for another allergic-type reaction. The zidovudine was prepared from a solution so that the concentration was 50 mg/5 mL. A desensitization protocol was carried out with once-daily dosing over 10 days. The initial dose was 1 mL or 10 mg. Subsequent doses were 20 mg, 50 mg, 80

mg, 100 mg, 120 mg, 150 mg, 200 mg, 250 mg, and 500 mg. The patient developed pruritus and a rash on the elbows and knees on the fifth and sixth days (doses were 100 mg and 120 mg). Administration of H_1 antagonists permitted continued administration of zidovudine. Eventually, the corticosteroid was discontinued, and the patient had no allergic manifestations over the next 8 months. This case exemplifies some of the issues involved with readministration of an essential but allergenic medication to a high-risk patient. The concurrent administration of methylprednisolone and H_1 antagonists did not overcome the drug hypersensitivity reaction. The initial dose was 0.02 of the final dose to try to avoid acute urticaria or anaphylaxis. One could not fault beginning with 0.01 of the final dose as has been suggested.

PRETREATMENT OF PATIENTS

Pretreatment of patients who have experienced previous, immediate, generalized reactions (e.g., acute urticaria, bronchospasm, angioedema, shock, and so forth) following infusion of radiographic contrast materials has been demonstrated to reduce the incidence of repeated reactions.¹⁹ The mechanism of the immediate generalized reactions from radiographic contrast materials remains unknown, but urine histamine concentration is elevated representing mast cell activation. A number of theories have been proposed, but the reactions remain idiosyncratic. The success of pretreatment of high-risk patients who must receive repeated infusions of radiographic contrast material has been extended to other clinical dilemmas, such as readministration of iron dextran,²⁶ a large polysaccharide that may induce immediate generalized reactions or serum sickness, plasma during platelet infusions,¹⁷ and protamine.²⁶ Pretreatment must be given over a sufficient period of time for the medications to work. Indeed, the best results to date have been with administration of prednisone 13 hours, 7 hours and 1 hour before and diphenhydramine and ephedrine (or albuterol) 1 hour before reinfusion of radiographic contrast material.¹⁷ Prednisone does not provide protection if administered within 2 hours of infusion of radiographic contrast material.²¹ When the untoward reaction is thought to be mediated by IgE antibodies or immune complexes, as occurs in serum sickness, oral corticosteroids have not necessarily been found to provide protection. In a study of patients with aplastic anemia who received horse antithymocyte globulin, serum sickness occurred despite patients receiving methylprednisolone 1 mg/kg per day from the beginning of the horse serum infusions.^{6, 22}

During desensitization protocols in which the patient is at high or low risk of developing an adverse drug reaction, it is advised, in most cases, to not pretreat with oral corticosteroids or H_1 antagonists. The emergence of erythema or limited urticaria, which is evidence of mast cell activation, should alert the physician that the dose already administered is a reactive one and that additional doses may precipitate a more severe allergic reaction. Should H_1 antagonists be used, these early warning signs may be absent and cause a false sense of security during challenges. When a patient with sporadic urticaria or dermatographism requires an incriminated medication, however, it is advisable to begin the challenge when there is no evidence of urticaria, pruritus, or erythema of the skin. In such patients, this author has administered H_1 antagonists to suppress the sensation of pruritus or urticaria so as not to confuse an episode of idiopathic urticaria with a medication reaction. The challenge of the patient may have to be delayed until the urticaria or dermatographism is suppressed just as a patient

with asthma who requires aspirin administration must have a baseline forced expiratory volume in 1 second (FEV₁) greater than 70% before the challenge.²⁶

PRECAUTIONS BEFORE DRUG CHALLENGE AND DESENSITIZATION PROTOCOLS

The physician considering the medication challenge should be familiar with issues surrounding such challenges as listed in Table 1. There may be additional issues in a specific situation. For example, the physician should have some understanding of the notion and practice of drug testing in patients who have been labeled as allergic, as well as awareness that the purported adverse reaction could be anxiety related. In the latter case, the medication is not truly contraindicated, and if the patient approves administration, the drug can be used. Hysterical symptoms should be identified and not be misinterpreted as laryngeal edema with subsequent unnecessary intubation. Whether or not test dosing or desensitization is carried out, the indication for the medication or diagnostic agent should be written in the medical record, and the patient should give verbal permission. In some cases, a family member or legal guardian must give consent for the challenge. The medical record should contain the patient's agreement to the challenge or desensitization. Ideally, a list will be prepared with places for medication doses and times of administration, physical findings (e.g., skin, lungs, and so forth), symptoms, vital signs, and relevant parameters relating to detection of the potential adverse reaction. Examples of selected drug challenges, pretreatment results if employed, and desensitization outcomes are listed in Table 3.

Before administration of the incriminated medication, planning should be made for treatment of adverse drug reactions or reactions to a diagnostic agent, such as radiographic contrast material. Emergency therapy should be available if the previous adverse reaction has been immediate in nature or where the history is consistent with an IgE-mediated reaction. Intravenous access should be established for most inpatient challenges unless the feared reaction is likely to be cutaneous in nature, such as a delayed erythematous, morbilliform eruption from sulfamethoxazole-trimethoprim in a patient with AIDS. For drug challenges and desensitization, the optimum setting is that of a patient who is not hypotensive or receiving dopamine or other supportive therapy. Nevertheless, some challenges must be performed in critically ill patients who are being ventilated mechanically or receiving medications to support systemic arterial blood pressure. Such patients may be in septic shock or respiratory failure and require a previously incriminated medication (e.g., piperacillin, vancomycin, sulfamethoxazole-trimethoprim, or pentamidine).¹⁸ After the indication is documented in the medical record, preferably by a physician who will not be performing the desensitization procedure, and consent is obtained, very cautious desensitization can be attempted. In cases in which penicillin skin testing can be carried out to assess current risk, that information should be obtained, but ultimately, the incriminated medication will be administered in a step-wise manner. In critically ill patients, this author favors intravenous testing so that changes in blood pressure or development of flushing or a rash can be detected quickly. A physician should remain at the bedside during the challenge because patients may develop precipitous declines in blood pressure. Alternatively, declines in blood pressure or a death from sepsis should not be attributed to anaphylaxis or drug hypersensitivity without sufficient clinical evidence.

Table 3. OUTCOME OF SELECTED DRUG CHALLENGES, PRETREATMENT REGIMENS, OR DESENSITIZATION PROTOCOLS

Condition	Desired Drug/Procedure	Outcome
Penicillin-induced anaphylaxis	Piperacillin for neutropenia	Penicillin major and minor skin test reactions were nonreactive; piperacillin was administered uneventfully
Penicillin-induced urticaria and mild wheezing	No allergy consult	Cefuroxime-induced respiratory failure
Radiographic contrast material induced shock and loss of consciousness	Coronary angiography	Prednisone–diphenhydramine pretreatment; iopamidol infusion uneventful
Radiographic contrast material shock in a neighbor; patient never had been exposed	Carotid angiogram	Same as radiographic contrast material; low-risk patient was terrified
Erythromycin caused neck to turn 90 degrees laterally	Erythromycin	Erythromycin test challenge caused neck to turn 90 degrees laterally
NSAID-induced urticaria and dyspnea	Ibuprofen for severe menstrual pain	Patient decreased room air oxygenation from 98% to 86% by decreasing tidal volume
Sulfamethoxazole–trimethoprim associated morbilliform rash 14 years previously	<i>Pneumocystis carinii</i> pneumonia treatment	Test challenge over 3 days was successful; morbilliform rash occurred on day 8, treated with prednisone for 4 weeks as the antibiotic was continued; no further rash over 5 months

SELECTED DRUG CHALLENGES

Mast Cell Activation Reactions

Administration of vancomycin in adults has been associated with mast cell activation and histamine release with detectable increases in plasma histamine concentrations.²⁸ In adults, infusions over 1 hour were carried out with 500 mg and 1000 mg, and increases in plasma histamine over baseline occurred in the latter group.²⁸ None of the 500 mg infusions was associated with the "red man" syndrome, but 9 of 11 patients experienced mast cell activation symptoms from the 1000 mg dose. Plasma histamine concentrations were elevated after the larger dose but not after the 500 mg vancomycin infusions. Rarely, vancomycin can cause Stevens-Johnson syndrome¹ or exfoliative dermatitis,²⁴ but most vancomycin allergy cases are a result of pruritus and urticaria that does not contraindicate the antibiotic. Some patients who have experienced the "red man" syndrome will develop pruritus despite infusion of vancomycin over the typical 1 hour period. Such patients should receive vancomycin over 2 to 8 hours, especially if they have a pre-existing dermatitis.²⁵ Some patients will have acute pruritus and benefit from a concurrent H₁ antagonist.

Opioid agents also can bind to mast cells and activate them, resulting in acute urticaria, angioedema, or pruritus.²⁶ From a historical basis, codeine has been injected intradermally during immediate skin testing as a positive control to demonstrate that mast cells can react if stimulated, in contrast to injections of histamine, which confirms that there are histamine receptors on blood vessels. Several alternatives exist for patients who have developed acute urticaria, upper airway obstruction, or other allergic reaction to morphine sulfate and may have experienced unacceptable nausea and vertigo from hydromorphone hydrochloride. One alternative is meperidine, but because of the serum peaks and valleys, it is going out of vogue. Another alternative for difficult-to-manage patients who report untoward reactions to a series of narcotic agents is fentanyl. For major pain control, fentanyl transdermally can be tried, although there is a delay in action, or it can be administered intravenously. For intravenous infusion, prepare 100 mL of a solution containing 10 µg/mL of fentanyl. To manage severe pain, in the first 30 minutes, infuse 5 to 10 mL (50–100 µg), and then reduce to 6 to 8 mL per hour (60–80 µg).

THE MULTIPLE DRUG ALLERGY PATIENT

Multiple drug allergy is defined by the report that a patient has incriminated several medications whose adverse reactions appear to be convincing in nature⁴ and not a series of intolerant responses. Symptoms such as urticaria, angioedema, bronchoconstriction, anaphylaxis, and Stevens-Johnson syndrome have been reported. From 120 patients evaluated because of an antimicrobial drug reaction, 23 (19%) were identified by reacting to at least one additional alternative antibiotic.⁴ Elective oral challenges were performed. Vancomycin testing was not performed, and only 3 elective challenges with sulfonamides were conducted. The frequency of positive antibiotic challenges in patients allergic to at least one antibiotic was as follows: clarithromycin 8 of 99 challenges (8%), pefloxacin 15 of 94 (16%), amoxicillin 3 of 20 (15%), lincomycin 9 of 24 (37%), doxycycline 7 of 13 (54%), and sulfamethoxazole–trimethoprim 1 of 3 (33%). In addition, 19 (15.8%) patients reacted to three or more antibiotics. Thirty patients (25%) reported urticaria or angioedema, exfoliative dermatitis, or Stevens-John-

son syndrome from nonsteroidal anti-inflammatory drugs (NSAIDs) and 15 of 36 (42%) patients were allergic to two or more antibiotics and were susceptible to NSAIDs. In contrast, 15 of 84 (18%) of single antibiotic allergic patients reacted to NSAIDs. These data illustrated that patients with multiple antibiotic allergies were more likely to react to NSAIDs. Finally, this study did not find that the presence of atopy was a risk factor for multiple drug allergy syndrome.⁴

In evaluating a patient with multiple allergic reactions, it is advisable to first record when the adverse reaction occurred and separate allergic or immunologic-in-type reactions from intolerance reactions, side effects, drug interactions, secondary effects of medications, and anxiety reactions. Next, determine what is the priority for possible skin testing to identify antimedication IgE antibodies to assess current risk and what medication might be required. Reassurance and reduced starting doses may be sufficient for patients who have experienced many adverse drug reactions that are intolerant rather than allergic in type. The urgency of the medical condition, the type and severity of the previous reaction, and the expertise of the physician in charge of the readministration are factors that dictate the speed of rechallenge or attempted desensitization. Examples of drug challenges with a cephalosporin or penicillin (Table 4), penicillin for syphilis (Table 5), and penicillin (Table 6) are provided for guidance. In some cases, a prior reaction, such as Stevens-Johnson syndrome or severe exfoliative dermatitis, is an absolute contraindication to rechallenge or desensitization because patient and physician safety must be preserved. Although this statement has been modified in management of selected patients with AIDS who have had adverse reactions to multiple medications, the principle remains that drug challenges and desensitization protocols should be designed to administer the incriminated medication as safely as possible. Early detection and therapy for immediate or delayed reactions should be a requirement to avoid more serious and potentially fatal adverse drug reactions.

Table 4. EXAMPLE OF A TEST-DOSING SCHEDULE FOR PENICILLIN OR CEPHALOSPORIN*

Rights were not granted to include this data in electronic media. Please refer to the printed journal.

From Rich RR: Clinical Immunology: Principles and Practice. St. Louis, Mosby, 1996, p 995; with permission.

Table 5. A SCHEDULE FOR DESENSITIZATION IN A PREGNANT WOMAN WITH SYPHILIS

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From Patterson R, DeSwarte RD, Greenberger PA, et al: Drug allergy and protocols for management of drug allergies. Allergy Proc 15:251, 1994; with permission.

Table 6. A REPRESENTATIVE INSULIN DENSENSITIZATION SCHEDULE

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From Patterson R, DeSwarte RD, Greenberger PA, et al: Drug allergy and protocols for management of drug allergies. Allergy Proc 15:252, 1994; with permission.

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Address reprint requests to

Paul A. Greenberger, MD
Division of Allergy-Immunology
Department of Medicine
Northwestern University Medical School
303 East Chicago Avenue, MC S 207
Chicago, IL 60611-3008

e-mail: P-Greenberger@NWU.edu