
Antibiotic desensitization for the allergic patient: 5 years of experience and practice

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Background: Antibiotic desensitization is an option for patients with suspected IgE-mediated antibiotic allergy when no other alternative exists for treating life-threatening bacterial infections. However, there are limited data describing the outcomes of this procedure with newer, commonly used antibiotics.

Objective: To evaluate the safety and utility of antibiotic desensitization.

Methods: We retrospectively reviewed the medical records of all patients undergoing antibiotic desensitization in our institution between November 1996 and November 2001.

Results: There were a total of 57 desensitizations performed in 21 patients. The mean age of the patients was 22.8 years (range, 1.9–44.5 years) and 15 (71%) were female. Nineteen (90%) of the 21 patients had been diagnosed as having cystic fibrosis. In 33 (100%) of 33 desensitizations to unique antibiotics that occurred during the study period, the indication for desensitization was a history suggestive of an IgE-mediated reaction to the antibiotic and/or a positive skin test result to the antibiotic or a known cross-reactive antibiotic. Desensitizations were performed to 12 different antibiotics. Successful outcomes were achieved in 43 desensitizations (75%). Of the 11 cases (19%) that were terminated due to an allergic reaction, there were no fatalities, intubations, or other aggressive interventions besides the use of epinephrine, antihistamines, and corticosteroids. In 7 of 11 unsuccessful desensitizations, a non-IgE mechanism appeared to be responsible for the allergic reaction.

Conclusions: Antibiotic desensitization is a useful option when treating patients with life-threatening infections who must receive antibiotics to which they have an IgE-mediated allergy. These data indicate that in most cases, patients with presumed IgE-mediated antibiotic allergy may safely receive antibiotics after desensitization.

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INTRODUCTION

Occasionally, physicians are confronted with treating patients infected with organisms sensitive only to antibiotics to which the patient is allergic. This situation is seen most commonly in patients with cystic fibrosis (CF). During their lifetime, CF patients receive multiple courses of antibiotics, which may predispose them to allergic sensitization against a range of antibiotics¹ while encouraging the selection of multidrug-resistant organisms.

Desensitization is a process designed to allow safe delivery of an antibiotic to a patient who has an IgE-mediated sensitivity to that drug. Desensitization is achieved by administering progressive doses of the drug until a full therapeutic dose is clinically tolerated.² The procedure entails risk of acute allergic reactions, including death, and should be performed only in a controlled inpatient setting, although there is debate about whether desensitization can be safely undertaken outside an intensive care unit.^{1,3–5} Desensitization is contraindicated for use in patients with a history of Stevens-Johnson syndrome (a vesiculobullous disease of the skin, mouth, eyes, and genitals) and severe exfoliative dermatitis.⁶

There is a body of literature describing the safety and utility of antibiotic desensitization, although most studies are small and often describe the use of a single antibiotic or single class of antibiotic.^{4,7–18} We reviewed the experience with desensitization to all classes of antibiotics in our institution during the 5-year period of 1996 to 2001 and have accumulated what we believe to be the largest combined series of antibiotic desensitization outcomes published to date. On the basis of this experience, we outline the process involved in selecting a candidate for antibiotic desensitization and present our standard protocols for desensitization for a range of common antibiotics used in CF patients.

MATERIALS AND METHODS

With the approval of the Committee on Clinical Investigation, we conducted a retrospective medical record review of patients undergoing antibiotic desensitization at Children's Hospital, Boston, MA, between November 1996 and November 2001. To maximize the breadth of data collected and avoid selection bias, lists of potential patients were obtained from multiple sources, including Allergy/Immunology Division records, intensive care unit admission records, and the pharmacy database. Any patient receiving antibiotic desensitization during this period was included in our analysis. Data collected included sex, admitting diagnosis, age at time of desensitization, history of reaction to the antibiotic, antibiotic skin testing results, and outcome of desensitization.

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Skin Testing Protocol

Penicillin skin test protocols were based on those published by the Joint Task Force on Practice Parameters.¹⁹ Briefly, patients underwent prick testing with penicilloyl polylysine (PrePen; 6×10^{-5} M), minor determinate mixture (MDM; a 10^{-2} M mixture of benzyl penicilloate, benzyl penicilloic acid, and penicillin G), penicillin G (10,000 U/mL), and ampicillin (25 mg/mL). If the prick test results were negative, full-strength intracutaneous tests were placed. Wheal sizes of 3 mm or greater and erythema greater than the negative control were considered positive results on both prick and intracutaneous tests.¹⁹ In some cases, a more cautious titration was undertaken for intracutaneous tests, starting with a 1:100 dilution. For nonpenicillin antibiotics, the concentrations used for skin testing were based on available nonirritating skin test concentrations.^{14,20-23}

Antibiotic Desensitization Protocol

During the review period, the protocols for desensitization to a range of antibiotics were taken from the literature and developed by Allergy/Immunology Division staff. In general, the protocols involved the same strategy of starting at 2 µg or 1/1,000,000 of the full therapeutic dose delivered by contin-

uous intravenous infusion of 30 minutes' duration and proceeding with 10-fold dose increases, all by continuous intravenous infusion of 30 minutes' duration, until the full therapeutic dose was reached. After desensitization, the patients received the full therapeutic dose at standard intervals until discharge. Generally, patients were not pretreated with antihistamines or corticosteroids before desensitization.

To ensure quality control and avoid errors, attempts have been made at our institution to standardize the antibiotic desensitization protocols. Figure 1 contains the standardized protocols and orders we have developed for the most common antibiotic desensitizations performed in our institution, namely, aztreonam, cefepime, ceftazidime, meropenem, piperacillin, and piperacillin-tazobactam.

Outcome Evaluation

Desensitization outcomes were divided into 4 groups: (1) successful, (2) mild cutaneous reaction with successful completion of desensitization, (3) failed desensitization in which the procedure was terminated due to evidence of a systemic allergic reaction, and (4) "other" in which use of the antibiotic was discontinued for reasons other than allergic reactions. In this study, 2 elements had to be met before a

Antibiotic:	Dose: (Cystic Fibrosis)	Maximum Dose:
Aztreonam	150 - 200 mg/kg/day ÷ q6h	8 g/day
Cefepime	150 mg/kg/day ÷ q8h	6 g/day
Ceftazidime	150 - 200 mg/kg/day ÷ q8h	6 g/day
Meropenem	60-120 mg/kg/day ÷ q8h	6 g/day
Piperacillin	300 - 500 mg/kg/day ÷ q6h	24 g/day
Piperacillin/Tazobactam	300 mg/kg/day ÷ q6h	18 g/day (as pip)

Desensitization Doses will be mixed with Normal Saline (NS). If different fluid needed, please specify _____

Infuse the following drug doses continuously over 30 minutes each. Rate = 1.66 mL/min or 100 mL/hour				
2 micrograms in 50 mL of NS, then				
20 micrograms in 50 mL of NS, then				
200 micrograms in 50 mL of NS, then				
2 mg in 50 mL of NS, then				
20 mg in 50 mL of NS, then				
200 mg in 50 mL of NS, then				
Aztreonam	Ceftazidime or Cefepime	Meropenem	Piperacillin	Piperacillin/Tazobactam
FTD of ____mg OR 2 g in 50 mL of NS	FTD of ____mg OR 2 g in 50 mL of NS	FTD of ____mg OR 2 g in 50 mL of NS	FTD of ____mg OR 2 g in 50 mL of NS	FTD of ____mg OR 2 g in 50 mL of NS
			FTD of ____mg OR 4 g in 50 mL of NS	FTD of ____mg OR 4.5 g in 50 mL of NS
Then continue Full therapeutic Dose (FTD): ____ mg IV Q____h after desensitization is complete until discharge.				

Figure 1. Standardized antibiotic desensitization protocol and physician orders. q indicates every; IV, intravenous; max, maximum; IM, intramuscular; as pip, dosed as piperacillin.

Verify availability of resuscitation cart and have the following medications at the bedside:

Epinephrine (1:1,000) 0.01mL/kg x ____kg = ____mL (max 0.5 mL/dose) IM x1
Diphenhydramine 1 mg/kg x ____kg = ____mg (max 50 mg/dose) IV x1
Methylprednisolone 2 mg/kg x ____kg = ____mg (max 60 mg/dose) IV x1
Normal Saline Bolus 20 mL/kg x ____kg = ____mL (max 1000 mL) IV x1
Albuterol Inhalation Solution 0.5 % 0.03 mL/kg = ____mL (max 1 mL) in 2 mL NS x 1
PLEASE PAGE ALLERGY FELLOW WITH ANY QUESTIONS:

Signature Allergy Fellow _____ Pager _____
House Officer _____ Pager _____

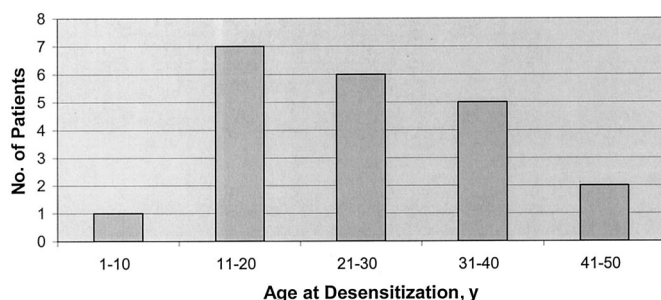


Figure 2. Patient age at desensitization.

desensitization was classified as successful. First, the patient had to complete the desensitization procedure without any reaction. Second, the patient had to be able to tolerate repeated administration of the full dose of the antibiotic without allergic reactions until the treating physician discontinued use of the medication.

RESULTS

Demographic Data

The mean age of the 21 patients who underwent desensitization during our study period was 22.8 years, with a range of 1.9 to 44.5 years (Fig 2). Fifteen (71%) of the patients were female and 6 (29%) were male. Nineteen (90%) had been previously diagnosed as having CF, whereas 2 (10%) of the patients had other diagnoses (scoliosis with infection of surgically placed rods and *Clostridium difficile* colitis, which was unresponsive to metronidazole therapy). During the study period, a number of the patients were desensitized on more than one occasion. Figure 3 shows the distribution of patients undergoing additional desensitization. A total of 57 desensitizations were performed during our period of study.

Antibiotics Used for Desensitization

Table 1 shows the list of antibiotics used for desensitization. This list is consistent with the range of antibiotics needed by patients with CF for their chronic lung infections. Fifty-six of the 57 antibiotic desensitizations were by continuous intravenous infusion as outlined in Figure 1. A patient with CF who required oral minocycline for coverage of *Burkholderia cepacia* undertook the single oral desensitization. Another patient who was allergic to vancomycin developed persistent *C difficile* colitis, which was unresponsive to metronidazole

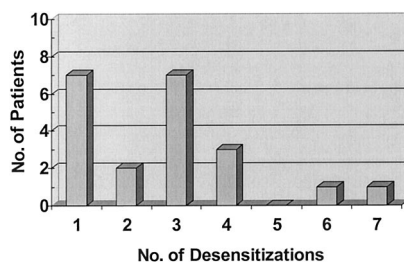


Figure 3. Number of patients receiving multiple desensitizations.

Table 1. Antibiotics Used for Desensitization

Antibiotic	No. of patients desensitized	No. of desensitizations	No. of successful desensitizations
Aztreonam	3	6	4
Cefepime	2	3	1
Ceftazadime	6	7	4
Ciprofloxacin	1	4	4
Gentamicin	1	1	0
Imipenem	2	2	1
Meropenem	3	4	4
Minocycline	1	1 (via the oral route)	1
Piperacillin	10	24	19
Piperacillin-tazobactam	1	1	1
Tobramycin	1	2	2
Vancomycin	2	2	2
Total	33	57	43

therapy. This patient was desensitized to vancomycin by the intravenous route and was subsequently converted to oral vancomycin to complete the treatment course.

Indications for Desensitization

There was evidence suggestive of an IgE-mediated reaction against the antibiotic that was delivered during the initial desensitization in 33 (100%) of the 33 individual antibiotic desensitization attempts in this study (Table 2). The presence of antibiotic-specific IgE was inferred by a combination of careful history taking and skin testing. The history was considered to be suggestive of an IgE-mediated antibiotic allergy if it included changes in the skin (urticaria, angioedema), respiratory status (lip or tongue swelling, hoarseness, difficulty swallowing, laryngospasm, stridor, increased respiratory effort, wheezing, cyanosis), cardiovascular system (hypotension), or gastrointestinal system (abdominal pain, vomiting, diarrhea) and if the reaction occurred within a period consistent with an IgE-mediated mechanism.

Table 2. Indications for Antibiotic Desensitization

Clinical History Suggestive of an IgE-Mediated Allergic Response	31 (94%)
-Positive skin test result to antibiotic or known cross-reactive antibiotic	18 (55%)
-Negative skin test result	6 (18%)
-No skin testing performed	7 (21%)
Other Indications	2 (6%)
-No history of penicillin exposure, but previous reaction to cephalosporin and positive penicillin skin test result	
Number of Desensitizations to Different Antibiotics	33

Most of the desensitizations in this study (55%) were performed on the basis of both a suggestive history and positive skin test result to the specific antibiotic or a known cross-reactive antibiotic.^{19,24} In 39% of the desensitizations, the indication was a history consistent with an IgE-mediated reaction alone, because either these patients had a negative skin test result or no skin testing was performed. For 2 (6%) of the procedures, there was no history of previous exposure to the antibiotic. A single patient accounted for the 2 desensitizations in this group. This patient had a history of an immediate reaction to ceftazidime and during evaluation for this reaction was skin test positive to penicillin G and minor determinate mixture. During the study period, she was desensitized to piperacillin and piperacillin-tazobactam.

Outcome of Desensitizations

Of the 57 desensitization attempts, 43 (75%) were completed safely and successfully, and these patients were then able to tolerate additional dosing of the antibiotic until discontinuation by their treating physicians (Fig 4). Thirty-seven of the desensitizations were successfully completed with no reactions, and 6 were complicated by only mild cutaneous reactions, allowing the desensitization to proceed to successful completion. Eleven (19%) of the attempts were terminated due to significant allergic reactions. Three (5%) were classified as other outcomes in which the procedure was discontinued for reasons other than allergic reactions.

Careful analysis of the patients in whom desensitization failed is arguably more important than evaluation of those who underwent the procedure without incident. Eleven (19%) of the antibiotic desensitizations were discontinued due to adverse reactions. Interestingly, a single patient accounted for 6 of the 11 unsuccessful desensitizations. This patient was a man with CF who was 23 years old at the time of the first attempted desensitization. On the basis of history and skin testing, he was believed to have IgE-mediated reactions against piperacillin, aztreonam, and imipenem. Attempts were made to desensitize him to each of these antibiotics. On one occasion, he experienced some cutaneous reactions but was able to complete the piperacillin desensitization protocol;

however, 7 to 10 days later he experienced abdominal pain, a rise in his liver enzyme levels, and a decrease in his serum complement levels that resolved with cessation of the antibiotic. He also experienced a decrease in serum complement levels after exposure to aztreonam. Another of the failures occurred in a patient who developed serum sickness 10 days after undergoing desensitization to ceftazidime.

In retrospect, it seems that 7 of the 11 failed desensitizations were in patients with reactions that were not solely IgE mediated. Review of the other patients in whom desensitization failed did not reveal any features that could be used to differentiate this group from those who tolerated desensitization. Three of the 4 failures occurred immediately during the desensitization procedure, with the patients developing typical clinical features of IgE-mediated anaphylaxis. The fourth failure was interesting in that the patient tolerated the standard vancomycin desensitization protocol, but when the first full dose was administered after the appropriate time interval, the patient developed anaphylaxis. All these patients responded well to standard treatment for anaphylaxis involving epinephrine, antihistamines, and corticosteroids.

DISCUSSION

We report what we believe to be the largest published series describing the outcome of desensitization to a wide range of commonly used antibiotics. Seventy-five percent of the procedures were completed safely and successfully, with the patients subsequently able to tolerate additional dosing of the antibiotic until discontinuation by their treating physicians. Nineteen percent of the desensitizations were terminated due to allergic reactions either during the desensitization procedure or with subsequent dosing of the antibiotic. Nevertheless, there were no fatalities and no patient required intubation or other aggressive interventions apart from standard medical therapy for anaphylaxis with a combination of epinephrine, antihistamines, and corticosteroids (Fig 4).

Our data are consistent with those of other groups,^{4,7-18} indicating that desensitization is an option for patients with a significant and potentially life-threatening infection amenable only to treatment with an antibiotic to which the patient has a documented allergy. One of the features of our study is that rather than focusing on desensitization to a single antibiotic, or a single class of antibiotics, we report on desensitization to 12 separate antibiotics (Table 1). In addition, the large age range of patients reported in this study (ie, 1.9 to 44.5 years; Fig 2) enhances the general relevance of these data. On the basis of our experience, we have developed standardized desensitization protocols to a range of antibiotics (aztreonam, cefepime, ceftazidime, meropenem, piperacillin, and piperacillin-tazobactam), which are commonly administered to patients with CF to treat their pulmonary infections (Fig 1). This information should prove useful for physicians considering the safety and utility of antibiotic desensitization for their patients who are allergic to a wide range of drugs.

The available evidence suggests that successful desensitization depends on achieving antigen-specific mast cell de-

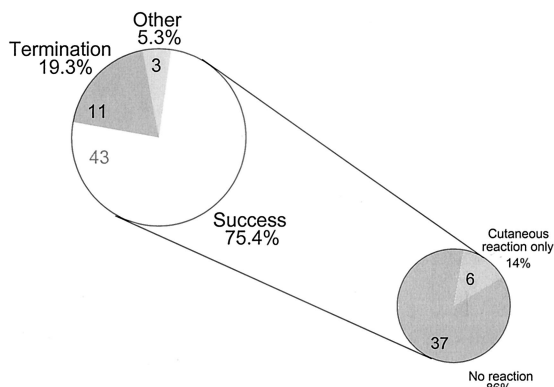
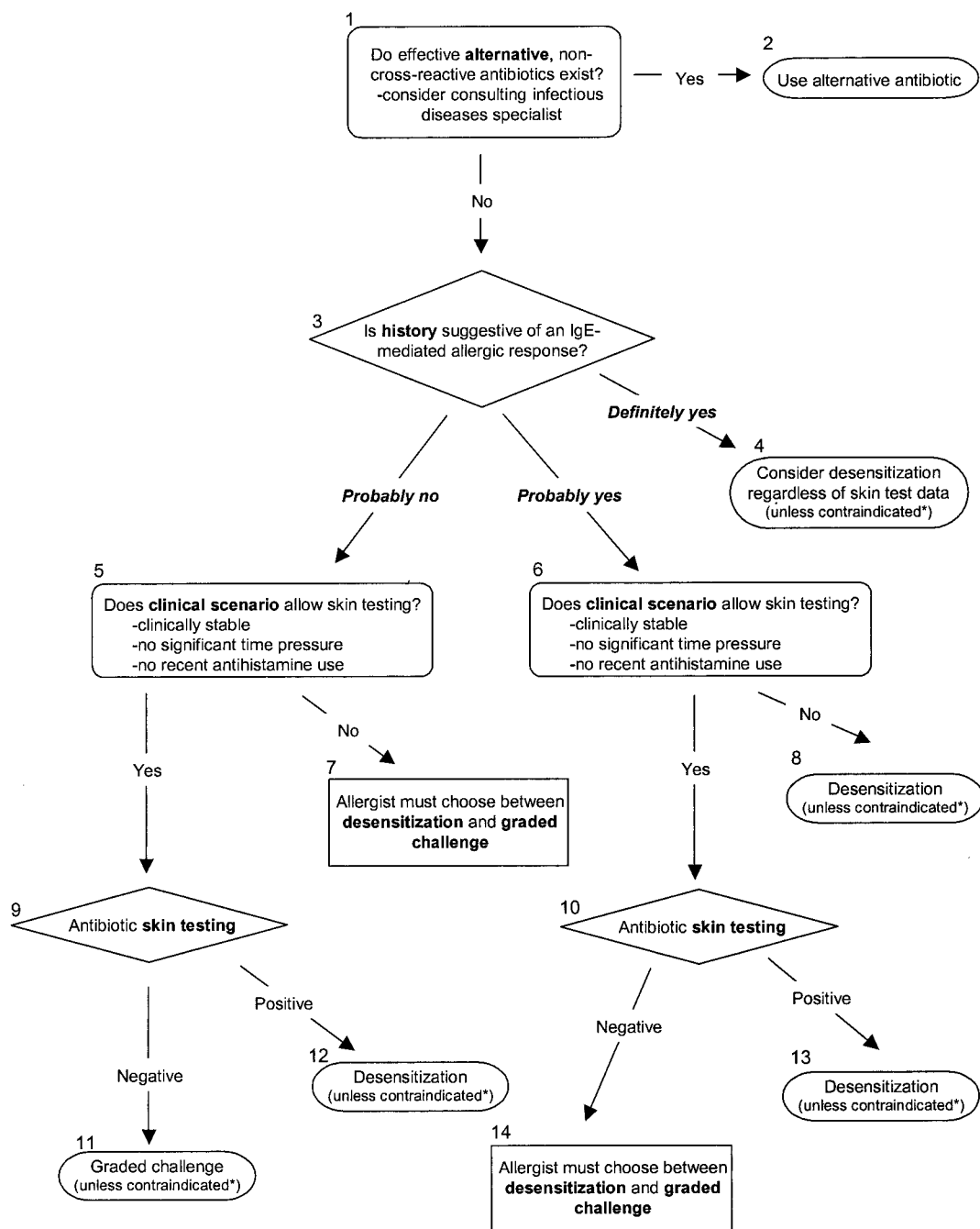


Figure 4. Desensitization outcomes.



* Contraindications for readministration of an antibiotic include a history of Stevens-Johnson syndrome and exfoliative dermatitis.

Figure 5. Stepwise approach to selecting patients for desensitization to antibiotics other than penicillin.

sensitization.^{11,14,25-27} Consequently, antibiotic desensitization is probably most useful in mitigating IgE-mediated, or type 1, allergic reactions. Nevertheless, sulfonamide desensitization has been successful in preventing delayed cutaneous reactions that are probably not IgE mediated.²⁸ In our study, the presence of antibiotic-specific IgE was inferred by a combination of careful history taking and skin testing. Although the utility of skin testing with penicillin and its major and minor determinants to demonstrate the presence of IgE is well established,^{19,29,30} the predictive value of skin testing with cephalosporins, monobactams, carbapenems, vancomycin, and other antibiotics remains unknown.^{3,19,31,32} Occasionally, useful information can be obtained by skin testing with dilutions of the native drug; however, until the immunochemistry of these antimicrobials is elucidated and the nonirritating concentrations of common antibiotics are established,^{14,20-23} these results must be interpreted with caution. The development of reliable assays to detect antibody-reactive IgE molecules will provide further assistance in selecting candidates for desensitization.³³

Our study suffers from the limitations that are inherent in a retrospective analysis. However, we believe our retrospective study design was unlikely to affect our principal outcome measure: evaluation of the safety and utility of antibiotic desensitization. Given that during the 5-year period of our study multiple physicians recommended that these patients undergo desensitization, it is likely that different standards were applied in determining whether an individual's history was thought to be consistent with an IgE-mediated response. We also suspect that there may be an element of selection bias in this study, insofar as if a patient had undergone desensitization once to a specific antibiotic, on subsequent admission it would be difficult for the consulting allergist to recommend giving that particular drug without additional desensitization. It is possible that a number of the patients who successfully underwent desensitization in our study period did not truly have an IgE-mediated allergy and as such may have been candidates for reintroduction of the antibiotic by cautious graded challenge. Nevertheless, until validated tests are available that allow us to accurately determine whether a patient is harboring IgE directed against a specific antibiotic, history and limited skin testing will be the mainstay in determining whether a patient should undergo desensitization.

A possible limit to the general applicability of our findings is that 19 (90%) of the 21 patients in this study had CF. However, this study is representative of the population most likely to be considered for antibiotic desensitization, and it seems unlikely that the nature of antibiotic hypersensitivity reactions in CF patients is significantly different from the general population.¹

On the basis of our clinical experience, we have created an algorithm that can be used when approaching a patient who may require antibiotic desensitization (Fig 5). This algorithm is only intended to assist in decision making for antibiotics other than penicillin, since reliable skin test reagents are available for penicillin. Although the algorithm is generally

self-explanatory, some elements deserve special mention. First, after obtaining a history of the patient's reactions to antibiotics, the clinician will have made an evaluation of whether the mechanism responsible for the adverse reaction is likely to be IgE mediated. In the algorithm, the arrows labeled "definitely yes," "probably yes," and "probably no" represent this clinical evaluation. Because guidelines such as this algorithm cannot replace sound clinical judgment, boxes 7 and 14 leave it up to the consulting allergist to choose between desensitization and a graded challenge, in which the antibiotic is reintroduced by gradual dose escalation (usually 1%, 10%, and 100% of the full therapeutic dose). Since a graded challenge is not designed to achieve mast cell desensitization, there is still a risk of anaphylaxis with this procedure, but the benefit is that after tolerating a graded challenge the patient and their physicians can generally be reassured that the patient is not allergic to the specific antibiotic.

In conclusion, this study demonstrates that antibiotic desensitization is a safe and useful therapeutic option for patients with life-threatening infections amenable only to antibiotics against which they have an IgE-mediated allergic response.

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