

Delayed Cutaneous Hypersensitivity Reactions to Antibiotics

Management with Desensitization



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KEYWORDS

- Antibiotic allergy • Delayed cutaneous adverse reactions • Desensitization • Management

KEY POINTS

- Mild to moderate delayed cutaneous adverse reactions to antibiotics can be successfully desensitized.
- Severe cutaneous adverse reaction to antibiotics is a contraindication to desensitization.
- Future research opportunities to the mechanism and protocol standardization for delayed cutaneous adverse reactions to antibiotics is needed.

INTRODUCTION

Drug reactions are a common event complicating patient care and can be immunologically mediated. Studies estimate that the incidence of drug reactions mediated by an immunologic mechanism is between 2.3 to 3.6 per 1000 patients, with almost all these reactions involving the skin and antibiotics being the most frequent precipitants of cutaneous reactions.^{1–4} The incidence of delayed drug reactions is not well characterized because most epidemiologic studies of cutaneous drug reactions are retrospective and firm demonstration of causality is difficult. One study estimates that Gel-Coombs type IV reactions account for approximately 25% of hypersensitivity reactions and 5% of all adverse drug reactions; however, other studies estimate that 64% of drug reactions are delayed.^{3,5} Management of patients with delayed cutaneous adverse reactions to antibiotics is mainly avoidance and use of alternative antibiotics. Alternatively, desensitization to an antibiotic that is suspected to have caused the delayed cutaneous adverse reactions has been described in the literature.

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This article explores the current literature of desensitization to delayed cutaneous adverse reactions to antibiotics.

PATHOPHYSIOLOGY

Given recent advancements in the understanding and management of drug allergy, a new classification system has been proposed by the recent PRACTALL guidelines to aid in the appropriate use of available testing and risk stratification.^{6,7} This new classification system involves dividing drug reactions by phenotype and endotype, rather than using the traditional Gel-Coombs classification system, which is cumbersome in the face of recent understanding of the diverse mechanisms of drug allergy.⁷ Here, phenotype refers to the timing of the drug reaction, with reactions occurring within 6 hours of administration as representative of immediate drug reactions, whereas reactions occurring in the days to weeks following administration are delayed.⁷ Drug reactions are further classified by endotype, which describes the mechanism through which the reaction occurs. For example, immediate onset of urticaria following administration of penicillin would have been classified as a Gel-Coombs type 1 reaction, which now would be understood as an immediate, immunoglobulin (Ig)-E-mediated drug allergy, whereas the classic reaction to abacavir would be described as a delayed, human leukocyte antigen (HLA)-associated drug reaction (Table 1). This allows more precise labeling of drug allergy as understanding of drug-mediated reactions increases.

Delayed drug reactions have a variety of manifestations and the pathways by which they occur have not been fully elucidated. Drug reaction with eosinophilia and systemic symptoms (DRESS), as well as maculopapular exanthema with eosinophilia, are manifestations of an eosinophil-mediated endotype, whereas Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are secondary to a cytotoxic T-cell-mediated endotype. Agranulocytosis exanthematous pustulosis (AGEP) is characterized by the formation of sterile pustules by neutrophil recruitment. The effects of delayed drug reactions can affect the liver, kidneys, and lungs, in addition to hematopoiesis; however, skin reactions are the most common manifestation. This is thought to be due to the presence of high numbers of primed cells of both innate and adaptive immunity in the skin.⁵ Due to the heterogeneous immune mechanisms that can precipitate a delayed adverse cutaneous drug eruption, there is diversity in the way drug reactions manifest in the skin. Maculopapular rashes are the most frequent, although life-threatening reactions are rare.⁴ The mortality rate of these reactions is 1% to 5% in SJS and up to 25% to 35% in TEN.⁸

Outside of genetic tests for certain HLA haplotypes that are associated with severe adverse cutaneous reactions, there is no validated testing to determine if a patient is

Table 1 Phenotypes and endotypes of drug allergy to trimethoprim sulfamethoxazole		
Reaction	Phenotype	Endotype
Anaphylaxis	Immediate	IgE-mediated
SJS	Delayed	Cytotoxic T cell
Maculopapular Rash	Delayed	Unknown
Serum Sickness	Delayed	Immune complex deposition
Aseptic Meningitis	Delayed	Possibly neutrophilic

Data from Refs.^{25,26,30,32,33}

going to experience a delayed drug reaction affecting the skin. Although skin prick testing (SPT) and intradermal testing (IDT) are widely used in IgE-mediated hypersensitivity reactions, their specificity is limited in delayed drug reactions.⁹ Patch testing has been proposed as a safe alternative to SPT or IDT; however, there is no positive control available and the negative predictive value is limited.⁹ In one case series, patch testing for penicillin-containing antibiotics showed high reproducibility for patients who had experienced a delayed reaction; however, this has not been borne out in other series.^{10–12}

MANAGEMENT

A desensitization procedure may be performed to induce tolerance to a culprit drug in a patient with a history of an immunologically mediated drug reaction. Desensitization has long been used to induce tolerance to life-saving antimicrobials but has increasingly been used in recent years for monoclonal antibodies and chemotherapeutic agents.^{13–19} In general, starting concentrations range from about 1 per 10,000 to 1 per 100 depending on the severity of the initial reaction.^{16,20} This dose is then often doubled over the course of minutes to several days. In immediate hypersensitivity reactions, it is thought that this induces a temporary state of tolerance in mast cells by binding to IgE at doses too low to trigger the activation threshold.²⁰ Most desensitization protocols have been published for immediate drug reactions; however, there is an increasing body of evidence that desensitization procedures can be applied in the context of delayed drug reactions.^{13,21,22} However, the mechanism of tolerance induction in delayed hypersensitivity reactions remains elusive but likely involves changes in the basophil and T-cell response.²³

There is a risk of inducing a hypersensitivity reaction when performing desensitization; therefore, appropriate patient selection is crucial. Desensitization is indicated when there is a lack of availability of therapeutic options of equivalent potency or efficacy. Desensitization is absolutely contraindicated in certain delayed reactions. These include vasculitis, hemolytic anemias, and DRESS, in addition to SJS or TEN, because there is a concern that even the small amounts of medication used in a desensitization protocol could possibly trigger one of these reactions and, unlike anaphylaxis, there is no known effective condition-specific treatment.²⁰ Desensitization is additionally relatively contraindicated in poorly controlled asthma.^{20,24} Due to the risk of a hypersensitivity reaction, desensitization procedures should be carried out under the supervision of staff trained to recognize and treat life-threatening hypersensitivity reactions promptly. Importantly, it should be emphasized that desensitization procedures induce tolerance only for as long as the medication is given regularly. Lapses in regular administration of the drug can result in an allergic hypersensitivity reaction. Before proceeding with desensitization, it should be emphasized with the patient and referring physician that desensitization does not confer tolerance in the long term and that adherence is crucial.

Amoxicillin and trimethoprim-sulfamethoxazole are widely used and very efficacious antimicrobials that also, unfortunately, have the highest rates of inciting both immediate and delayed hypersensitivity reactions.^{1,3,4} Indeed, one study found that trimethoprim-sulfamethoxazole was implicated in 66.6% of cutaneous drug reactions requiring hospitalization.⁴ Delayed drug reactions to both amoxicillin and trimethoprim-sulfamethoxazole have diverse manifestations, reflecting a variety of endotypical mechanisms that are often poorly understood. Trimethoprim-sulfamethoxazole is most notorious for precipitating SJS or TEN, which is mediated by cytotoxic T-cell mechanisms as well as a delayed maculopapular rash, the

mechanism of which is unknown.^{25,26} Penicillin-containing antibiotics have also been reported to cause SJS or TEN, as well as AGEP and fixed-drug eruptions.^{27–29} Serum sickness secondary to immune complex deposition has occurred in the context of trimethoprim-sulfamethoxazole and penicillins.^{30,31} Aseptic meningitis has also been reported to trimethoprim-sulfamethoxazole, which is possibly mediated by a neutrophilic reaction.³²

The literature is somewhat lacking regarding desensitization to nonimmediate reactions to antibiotics; however, in the case of trimethoprim-sulfamethoxazole, given its wide use and its predilection for causing cutaneous adverse drug reactions, numerous desensitization protocols have been published in both human immunodeficiency virus (HIV)-infected populations and non-HIV infected populations.^{21,24,34–41} Many trimethoprim-sulfamethoxazole case reports and series, unfortunately, do not differentiate between immediate and delayed-type hypersensitivity reactions, though many of the published cases involve apparent delayed cutaneous drug reaction.

One of the first case reports detailing successful trimethoprim-sulfamethoxazole desensitization over 6 weeks involved a patient with fever, rash, and joint pain.⁴² The clinical history presented in this case raises suspicion for serum sickness or other delayed reaction.⁴² In a paper on desensitization-graded challenge by Demoly and colleagues,⁴³ 2 of the 44 initially desensitized subjects developed maculopapular rash and fever on day 10 of trimethoprim-sulfamethoxazole therapy, 1 of whom was successfully desensitized at a later date with a 10-day protocol (Table 2). In a case series by Caumes and colleagues,³⁵ at the initial adverse drug reaction, the median time of rash onset was 10 days after initiating therapy; 37 of the 48 subjects who underwent the 8-step, 2-day protocol were successfully desensitized.

There are 2 case series reported that detail convincing delayed-drug reaction histories with reports of successful desensitization to trimethoprim-sulfamethoxazole. Kalanadhabhatta and colleagues³⁸ included at least 3 subjects with delayed drug eruption in their 1996 trimethoprim-sulfamethoxazole desensitization case series

Table 2 One-day trimethoprim-sulfamethoxazole graded administration protocol: 12 steps	
Step	Dose (mg)
1	0.001/0.0002
2	0.003/0.006
3	0.009/0.0018
4	0.03/0.006
5	0.09/0.018
6	0.3/0.06
7	1/0.2
8	3/0.6
9	9/1.8
10	30/6
11	90/18
12	300/60

Dosing interval is 30 minutes apart.
Adapted from Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998;102(6 Pt 1):1034; with permission.

(Table 3). Three of the subjects profiled in that study had onset of maculopapular rash 7 to 14 days after initiation of trimethoprim-sulfamethoxazole; all 3 of these subjects were successfully desensitized using a 3-phase, 36-step regimen.³⁸

Pyle and colleagues²¹ presented the largest case series of trimethoprim-sulfamethoxazole desensitization in subjects without HIV. Most of these subjects had nonurticarial rashes reported as their primary adverse drug reaction.²¹ Three desensitization protocols were studied, including 2 1-day protocols. One of these was a 6-step protocol starting at 0.004 mg of trimethoprim and 0.02 of sulfamethoxazole and using flexible intervals from 15 to 60 minutes based a previously published protocol by Gluckstein and Ruskin.^{21,37} The other 1-day protocol, modified from the Kalanadhabhatta and

Table 3 One-day trimethoprim-sulfamethoxazole graded administration Protocol: 3 Phase, Multi-Step		
Phase	Step	Dose (mg/mL)
Phase 1: 15-min dosing interval	1	0.000004/0.00002
	2	0.000008/0.00004
	3	0.000016/0.00008
	4	0.000032/0.00016
	5	0.00004/0.0002
	6	0.00008/0.0004
	7	0.00016/0.0008
	8	0.00032/0.0016
	9	0.0004/0.002
	10	0.0008/0.004
	11	0.0016/0.008
	12	0.0032/0.016
	13	0.004/0.02
	14	0.008/0.04
	15	0.016/0.08
	16	0.032/0.16
	17	0.04/0.2
	18	0.08/0.4
	19	0.16/0.8
	20	0.32/1.6
	21	0.4/2
	22	0.8/4
	23	1.6/8
	24	3.2/16
	25	4/20
Phase 2: 30-min dosing interval	1	8/40
	2	16/80
Phase 3: 2-h dosing interval	1	16/80
	2	16/80
	3	16/80
	4	16/80
	5	24/120
	6	40/200
	7	64/320
	8	80/400
	9	80/400
	10	80/400

Adapted from Kalanadhabhatta V, Muppidi D, Sahni H, et al. Successful oral desensitization to trimethoprim-sulfamethoxazole in acquired immune deficiency syndrome. *Ann Allergy Asthma Immunol* 1996;77(5):397; with permission.

colleagues 1996 protocol,³⁹ involved a 14-step, 4 hour desensitization starting a dose of 0.08 mg of trimethoprim and 0.016 mg of sulfamethoxazole.²² These studies offer the most convincing evidence of the success of desensitization in a delayed reaction to trimethoprim-sulfamethoxazole.

Unfortunately, there are no published case series on successful desensitization to amoxicillin after a delayed drug reaction, though successful desensitization has been reported for several other antibiotics. Most of the literature available on desensitization in the setting of penicillin hypersensitivity involves immediate reactions to penicillin.^{44–49} However, there have been 2 case series from the cystic fibrosis literature that offer evidence of successful desensitization in the case of delayed drug eruption secondary to antibiotics. In 2011, Whitaker and colleagues⁵⁰ published a retrospective review of 275 desensitizations in a population of 42 adult subjects with cystic fibrosis. In this population, repeat desensitizations to different antimicrobials are needed due to frequent infections from resistant organisms. Subjects were included if they experienced a drug reaction without typical IgE-mediated features that occurred greater than 24 hours after the antibiotic was initiated.⁵⁰ These subjects reported reactions to tazocin, ceftazidime, meropenem, aztreonam, tobramycin, and colomycin.⁵⁰ Multiple desensitizations were performed on the same subjects.⁵⁰ Using a 7-step, 2-hour and 20-minute procedure that involved 10-fold increases with each step, a 91% success rate was achieved, with success defined as successful completion of the antibiotic course.⁵⁰ In another retrospective study of 19 subjects with cystic fibrosis, 71 desensitization procedures were performed.⁵¹ The classes to which these desensitizations were performed included penicillins, cephalosporins, carbapenems, monobactams, vancomycin, sulfonamides, chloramphenicol, quinolones, and colomycins.⁵¹ This case series included 18 cases of delayed reaction. Of the 71 desensitization procedures that were performed, 76% were successful, though it is unclear how many of these successful desensitizations involved delayed reactions. These studies, particularly Whitaker and colleagues,⁵⁰ offer the most convincing evidence of the successful use of rapid desensitization protocols in the setting of delayed drug reactions.

Given the prevalence of delayed reactions to antimicrobials, as well as the potential life-saving value of successful desensitization to these essential medications, it is encouraging that rapid desensitization protocols have shown success in allowing subjects to tolerate various classes of antimicrobials that previously incited delayed reactions.^{21,35,38,50,51} In the study by Pyle and colleagues,²¹ the short-term and long-term (defined as a mean follow-up time of 11 months) success rates of both the 14-step and the 6-step protocols exhibited a success rate of 98%, whereas the short-term and long-term success rates of the 10-day protocol were 93% and 81%, respectively. The rate of adverse reactions was greater in the multiday protocol, and only one short protocol desensitization needed to be stopped secondary to an adverse event that consisted of a rash and lip swelling.²¹ Similarly, Whitaker and colleagues⁵⁰ using their 7-step, 2-hour and 20-minute protocol were able to achieve a 91% successful desensitization rate, with these subjects able to tolerate the antibiotic for the duration of its course. The reactions that lead to failure of desensitization were all reported as mild; many of these patients were able to tolerate desensitization to another antimicrobial.⁵⁰ These studies show that rapid desensitizations to antimicrobials lasting between 2 and 4 hours result in desensitizations that are not only safe and durable, but also more convenient for the patient.

The authors offer a basic outline of a rapid desensitization protocol to be used for various classes of antimicrobials, based on the work of Pyle and colleagues,²¹ Whitaker and colleagues,⁵⁰ and the 12-step to 16-step protocol for desensitization

Table 4
One-day trimethoprim-sulfamethoxazole graded administration protocol: 14 steps

Step	Dose (mg)
1	0.08/0.016
2	0.16/0.032
3	0.32/0.064
4	0.64/0.128
5	1.28/0.256
6	2.5/0.512
7	5/1
8	10/2
9	20/4
10	40/8
11	80/16
12	160/32
13	320/64
14	440/88

Dosing interval is 15 minutes apart.

Data from Pyle RC, Butterfield JH, Volcheck GW, et al. Successful outpatient graded administration of trimethoprim-sulfamethoxazole in patients without HIV and with a history of sulfonamide adverse drug reaction. *J Allergy Clin Immunol Pract* 2014;2(1):52–8.

pioneered by Dr. Castells' group,^{13,16,24} the general principles of desensitization outlined in the position paper on desensitization by Cernadas and colleagues,²⁰ and the position paper by Scherer and colleagues.⁵² With the success of short protocols, the authors propose a 14-step protocol with 15 minutes between each dosing interval (the safety and efficacy of rapid protocol is previously delineated).^{21,50} The initial concentration of antibiotic should be 1/1000 to 1/10,000 of the full-strength dose (Table 4).^{16,20,21} Doses should be doubled at 15-minute intervals because this dosing strategy has been proposed to trigger inhibitory mechanisms in immediate hypersensitivity reactions and are, perhaps, associated with less side effects than 10-fold increases.^{20,23} If this strategy fails, it may be prudent to proceed with a multiday desensitization approach, such as the 10-day protocol outlined by Pyle and colleagues²¹ and inspired by the 1994 protocol by Absar and colleagues,³⁴ which involves daily dose doubling. Although there is uncertainty as to how desensitization in the context of delayed drug reactions works, these studies provide evidence that temporary induction of tolerance is indeed possible.

As previously detailed, absolute contraindications to this protocol and all desensitizations include a history of severe exfoliative dermatosis, including SJS or TEN, as well as vasculitis, autoimmune cytopenias, and DRESS. Desensitization should only be performed with on-site staff that is trained in the management of acute hypersensitivity reactions.

SUMMARY

These cases illustrate that desensitization in patients with a history of delayed drug reaction is possible, though the mechanism remains unclear. The existing evidence is limited by underreporting of unsuccessful desensitizations; additionally, true sensitization is unconfirmed in most case series. Further prospective studies are needed to

further establish the role of desensitization in cases of delayed cutaneous drug reactions.

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