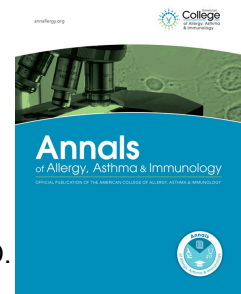


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**Hypersensitivity to tetracyclines: skin testing, graded challenge,
and desensitization regimens**

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1 Introduction

2 Tetracyclines are commonly used antimicrobials with a broad spectrum of activity
3 against a variety of organisms. Doxycycline and minocycline are the most commonly used
4 medications in this class of antibiotics. Glycylcyclines, including tigecycline, are newer
5 tetracycline-derived antibiotics that share similar antimicrobial activity with older tetracyclines.
6 Molecular changes to its parent molecule, minocycline, have augmented tigecycline's
7 antimicrobial activity and decreased its susceptibility to bacterial resistance.² In general,
8 tetracyclines are effective against many pathogens such as *S. pneumoniae*, *H. influenza*, and
9 methicillin-resistant staphylococcus aureus (MRSA), and they are often the preferred agents for
10 treatment of *Mycoplasma*, *Rickettsia*, *Chlamydia*, *Vibrio*, and *Ehrlichia* infections.¹ Due to their
11 widespread utility, tetracyclines are commonly prescribed, and are sometimes implicated in drug
12 hypersensitivity reactions (HSRs).

13 Although adverse reactions involving IgE-mediated mechanisms to these medications are
14 rarely reported,³ there have been case reports of anaphylaxis to both doxycycline⁴ and
15 minocycline.⁵ IgE-mediated HSRs may include urticaria, angioedema, rash, abdominal pain,
16 bronchospasm, respiratory distress and hypotension.^{4,5} Non-IgE-mediated reactions comprise
17 the majority of HSRs to the tetracycline class. Drug fever without rash has been described for
18 minocycline.⁶ Tigecycline-induced drug fever and leukemoid reaction has been described,
19 likely also with a non-IgE-mediated mechanism. Other non-IgE-mediated HSRs include DRESS,
20 papulosis, and serum sickness-like reactions or systemic lupus erythematosus.⁷⁻¹⁰

21 The rate of cross-reactivity between tetracycline antimicrobials has not yet been
22 established, but co-allergy to doxycycline and minocycline has been reported.¹¹ Differences in
23 side chain structures are hypothesized to be responsible for the different reaction rates.³ In

general, HSRs are more commonly attributed to minocycline than to doxycycline. A large case series in France demonstrated a lower incidence of drug reactions to doxycycline than to minocycline, with 3 patients having HSRs to doxycycline and 38 having HSRs to minocycline over a 12 year period.⁷

For certain infections, such as MRSA and tick-borne diseases, tetracyclines are some of only a few effective antimicrobials available, and in some cases, such as for Lyme disease, represent first-line therapy.¹² Therefore, even with a history of HSR, the use of these antibiotics may be warranted in such cases. Despite the necessity of tetracyclines and glycylcyclines as the first-line agents against many infections, guidelines for the evaluation and management of patients who suffer HSRs to these medications are not published.

Validated skin testing protocols, drug challenge procedures and rapid desensitization techniques are paramount for the evaluation and management of the growing population of patients with HSRs to the tetracyclines and tigecycline. Skin testing protocols and minimum non-irritating concentrations for doxycycline, minocycline and tigecycline have not been established. Furthermore, there have only been a few single case reports of doxycycline desensitization protocols, and these were all in adult patients.¹³⁻¹⁵ There are no previously reported validated desensitization protocols for use in pediatric patients. Additionally, to our knowledge, desensitization protocols for minocycline and tigecycline have not been previously reported.

Here, we present a case series of 10 patients, including 8 pediatric patients, with HSRs to doxycycline, minocycline and tigecycline (**Table I**). We describe the skin testing protocols we have created and implemented. We then present our graded challenges and well-tolerated desensitization procedures. In our case series, all patients successfully completed either their graded challenge or rapid desensitization.

Methods

We performed a retrospective chart review of patients with HSRs to tetracyclines and tigecycline who underwent skin testing, graded challenge and desensitization at Boston Children's Hospital between 2011 and 2019. Institutional Review Board approval was obtained.

Skin Testing Protocols

Skin prick and intradermal testing was performed at least 4 weeks after the initial reaction to reduce the likelihood of false negative results.¹⁶ Histamine (10 mg/mL) and saline were used as positive and negative controls respectively. The minimum non-irritating concentration for these antimicrobials has not been previously reported. As such, protocols were designed based on the maximum non-irritating concentrations of each antibiotic after testing between one and three control subjects. For the concentrations used for skin testing, see **Table II**.

Graded Challenge Procedures

If skin testing was negative, and the initial reaction was not severe based upon the Brown Classification Criteria,¹⁸ graded challenge to the culprit drug was performed.

Prior to graded challenge or desensitization, informed consent was obtained and the patient was admitted to a highly monitored unit, either intermediate or intensive care, depending on the severity of the initial reaction. Rescue medications, including intramuscular epinephrine, intravenous diphenhydramine, normal saline, albuterol and methylprednisolone were immediately available at the bedside in the event of an IgE-mediated reaction. In all cases, the

challenge entailed dosing 1% of the goal dose, followed 30 minutes later by 10% of the goal dose, followed 30 minutes later by 90% of the goal dose. The patient was monitored for at least one hour after the challenge for signs of intolerance.¹⁷

Desensitization Approach – Premedication Selection

If skin testing was positive and/or the reaction considered moderate or severe by the same criteria,¹⁸ desensitization was pursued with the same precautions as described above. Pre-treatment medications were utilized in select cases to minimize breakthrough reactions during the procedure and were implemented in cases with more severe initial reactions or in patients with history of previously failed desensitization procedures to other drugs. Pre-medications were determined based on the clinician's preference and/or concern for reaction during the desensitization. The pre-medication regimens were administered one hour prior to the start of the desensitization.

Desensitization Approach – Protocols

Patients B, E, and F were desensitized to oral doxycycline following the protocol in **Table III**. Patients A, F, and G were desensitized to oral minocycline following the protocol in **Table IV**. Patients A, and F were desensitized to intravenous tigecycline following the protocol in **Table V**.

Desensitization Approach – Management of Breakthrough Reactions

If breakthrough reactions occurred, they were addressed by temporarily pausing the protocol, treating the reaction and continuing after reducing the infusion rate or adding steps to the protocol.

Results

Characteristics of the patients are shown in **Table I**. Ten patients were evaluated for reactions to tetracyclines and tigecycline. The patients required the antibiotics for Lyme disease, cellulitis, or exacerbations of cystic fibrosis. Erythematous maculopapular rashes during tetracycline or tigecycline exposure were reported by patients A, B, C, D, G, H, and I. Although patient H's rash was concerning for DRESS while receiving tigecycline, she had been on multiple antibiotics at the time and tigecycline was not considered the most likely culprit for the reaction. Patient J reported urticaria during doxycycline treatment. More severe, likely IgE-mediated reactions were reported as well; patient E developed anaphylaxis during treatment with doxycycline for Lyme meningitis, and patient F developed chest tightness and bronchospasm with minocycline and tigecycline exposure, respectively.

Nine of the ten patients underwent skin testing to the culprit medication and to other antibiotics within the class if there was a potential need for these medications in the future. In summary, skin testing to doxycycline, minocycline and tigecycline was completed by seven, six and one patient respectively. In two cases, patients E and F, skin testing was initially deferred due to urgent need for the culprit medication. In patient E, skin testing was performed and was positive when performed six months after the patient underwent initial desensitization. Patient F had end-stage cystic fibrosis and in each case, prompt institution of life-saving antibiotics was

required prior to completion of skin testing. Desensitization was successfully completed to doxycycline, minocycline and tigecycline.

When the reaction history was not classified as moderate or severe and skin testing was negative, graded challenges were initiated. Graded challenges occurred to doxycycline in three patients (A, H and I); to minocycline in two patients (C and D); and tigecycline in two patients (A and H), and were successful in all.

In total, three desensitizations occurred to doxycycline, four to minocycline, and two to tigecycline. All desensitizations were completed successfully.

Pre-medications were only utilized in patient E. The patient was diagnosed with Lyme meningitis, and IV ceftriaxone started as first-line therapy; however, on day 9 of therapy the child developed a pruritic rash that mandated cessation of this antibiotic. Desensitization to ceftriaxone was attempted; however, she developed anaphylaxis during that protocol. Upon beginning doxycycline instead, she developed angioedema of the lips, facial flushing and abdominal upset. Desensitization was necessary, as there was no other appropriate antibiotic. Pre-medication with oral prednisolone and cetirizine was instituted due to her recent history of anaphylaxis during attempted ceftriaxone desensitization.

Two patients had breakthrough symptoms during the desensitization. Both of those breakthrough reactions were easily managed, allowing for successful continuation of desensitization and subsequent completion of treatment. Patient B was diagnosed with Lyme arthritis and tested positive by intradermal testing to all oral potential therapies, including amoxicillin and doxycycline. Doxycycline was recommended as first-line therapy for his Lyme arthritis. A 12-step desensitization to oral doxycycline was devised (**Table III**), with initial dose for the desensitization based on the concentration the patient reacted to during skin testing. The

child suffered mild pruritus localized to the shoulder during the final steps of the protocol, but this resolved with skin cooling measures. The patient received the next full dose of 100 mg twelve hours after the desensitization was started as prescribed and completed his four-week treatment course without incident.

Despite pre-medication, Patient E, who had Lyme meningitis, developed brightly erythematous cheeks without other associated symptoms immediately following the 6th dose (1 mg) of her doxycycline desensitization. The desensitization was paused for thirty minutes and she was administered oral diphenhydramine and montelukast. After this period of monitoring, an additional 1 mg dose was repeated as the new step 7, in an effort to improve the child's tolerance. The desensitization was then completed successfully without additional complications.

Discussion

Despite their common use and first-line indication for many infections, there is paucity in the literature regarding management of HSRs to tetracyclines and tigecycline. To our knowledge, this is the first comprehensive case series describing both pediatric and adult patients with HSRs to tetracyclines, their evaluation and management. This represents the first publication of skin testing, graded challenge and entirely oral desensitization protocols to this class of medication. In addition, while doxycycline and minocycline HSRs and anaphylaxis have been reported,^{4, 5, 7, 11} we believe this to be the first report of IgE-mediated reaction and desensitization to tigecycline.

In evaluating cases of HSR to tetracyclines, it is imperative to first attempt to define the mechanism behind the initial reaction (IgE or non-IgE mediated) and understand its severity. Pursuing skin testing in appropriate cases can then assist the allergist in choosing to perform a diagnostic graded challenge or a therapeutic desensitization procedure. Although skin prick

testing has been reported to minocycline,¹⁹ to our knowledge our report offers the first intradermal skin testing protocols for these antibiotics. The non-irritating concentration of the medication is used as a point of reference in developing skin testing regimens.²⁰ However, the maximum non-irritating concentration of doxycycline, minocycline and tigecycline has not been reported. Therefore, we tested control subjects for each of the antimicrobials described in order to determine the non-irritating concentration of the medication.

In cases in which the medications are needed immediately, skin testing may not be feasible prior to administration. Furthermore, if the index reaction occurred recently, the probability of false negative skin testing may be increased.¹⁶ However, skin testing may be useful to inform future antibiotic use and can be completed at least a few weeks after desensitization to mitigate the risk of a temporary false negative result.

Patient B and E with Lyme arthritis and Lyme meningitis, respectively, underwent urgent desensitization without prior skin testing. Subsequently, skin testing was completed to guide future antimicrobial treatment. The one patient who did not have skin testing completed, Patient F, required the antibiotics urgently during exacerbations of end-stage cystic fibrosis and unfortunately passed away before skin testing could be completed.

The skin prick testing regimens we developed had excellent negative predictive value for five patients (Patients A, C, D, H and I). Each of these patients, whose initial reactions were not severe, successfully tolerated doxycycline, minocycline or tigecycline graded challenges after negative skin testing.

The case of Patient H deserves special attention. The general approach in cases of DRESS is strict avoidance. However, in rare cases like this patient's, when multiple medications are involved and treatment with one of the medications that was not likely to be the culprit is

medically necessary, and no other alternative medications are available, then graded challenge may be considered.

The true positive predictive value of the initial skin testing for Patient B, who had Lyme disease is less clear. This patient had positive intradermal skin tests to all of the anti-Lyme antibiotic therapies tested, including penicillin, ampicillin, doxycycline, cefuroxime and ceftriaxone. Jarisch-Herxheimer reactions have been described with treatment of Lyme disease,²¹ and this reaction could explain his reactions to both doxycycline and amoxicillin. However, this reaction is typically accompanied by fever, rigors, and vital sign changes in addition to rash, which our patient did not exhibit. Given the positive skin tests and immediate need for the medication, Patient B was successfully desensitized to doxycycline. His mild pruritus during the desensitization supports a propensity toward a histamine-release with doxycycline exposure. Additionally, approximately two years after initial skin testing, Patient B's skin testing was repeated to the same antibiotics, and intradermal testing remained positive to ampicillin and doxycycline, but was negative to the cephalosporins tested, including ceftriaxone and cefuroxime.

When patients had positive skin testing, as was the case for Patients A, B, E, and G, desensitization procedures as described above and in **Tables III-V** were successfully performed. Such procedures are thought to be most effective in IgE-mediated reactions, however desensitization has also been used successfully previously in HSRs that are non-IgE-mediated.²² Desensitization was well tolerated by patients A and B who had initial reactions that were delayed in onset and unlikely to be solely IgE-mediated. Furthermore, these patients completed their recommended treatment course without delayed reaction. Overall, these protocols were well

tolerated when used in both adult and pediatric patients and only one patient required amendment of the protocol due to a reaction consistent with IgE-mediated hypersensitivity.

While there are several case reports involving desensitization to doxycycline which involve protocols that are at least initially intravenously administered, to our knowledge, ours is the first published protocol in which the desensitization to this antibiotic is entirely enteral. Furthermore, our protocols to minocycline and tigecycline represent the first in the literature and were well-tolerated by both pediatric and adult patients. An allergist must carefully customize the pre-medication regimen to the specific patient. A clinician's judgement must also be employed in the management of breakthrough reactions, should they occur.

In summary, this literature represents the first comprehensive description of HSRs to tetracyclines in adult and pediatric patients, their evaluation including skin testing regimens, and their management with graded challenge procedures or desensitization protocols. To our knowledge, these protocols are novel and valuable to clinicians caring for pediatric and adult patients with a history of HSRs to this class of antimicrobials. In all cases, graded challenge or desensitization was safely completed. Assessing the severity of the index reaction, implementing skin testing when safe, and pursuing graded challenge or desensitization based on the data available can facilitate use of first-line pharmacologic therapy to patients with HSRs to tetracyclines.

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Patient	Age Sex	Indication	Reaction History	Severity	Skin Testing	Procedures	Outcome
A	13F	CF exacerbation	Minocycline: developed pruritic maculopapular rash, on day 4 of therapy, resolved with drug cessation	Mild	Doxycycline: Negative	Doxycycline: Graded Challenge	Successful
			Tigecycline: no prior trial, GC completed due to severity of minocycline allergy		Minocycline: Positive	Minocycline: Desensitized Tigecycline: Graded Challenge	
B	12M	Lyme Arthritis	Doxycycline: pruritic maculopapular rash on day 5 of therapy.	Mild	Doxycycline: Positive	Doxycycline: Desensitized	Successful
C	17F	CF exacerbation	Tolerated doxycycline Minocycline: generalized, pruritic, maculopapular rash on day 9 of therapy	Mild	Minocycline: Negative	Minocycline: Graded Challenge	Successful
D	68F	Cellulitis	Tetracycline: Pruritic, erythematous rash	Mild	Doxycycline: Positive	Minocycline: Graded Challenge	Successful
					Minocycline: Negative		
E	7F	Lyme Meningitis	Doxycycline: angioedema of lip, facial flushing, abdominal upset	Mod.	Doxycycline: Positive	Doxycycline: Desensitized	Successful
					Minocycline: Positive		
F	40F	CF exacerbation	Doxycycline: no prior use, desensitized due to severity of other tetracycline reactions Minocycline: chest tightness, oral tingling Tigecycline: bronchospasm day 17	Mod.	Deferred due to urgency of illness	Doxycycline: Desensitized Minocycline: Desensitized Tigecycline: Desensitized	Successful
G	20F	CF exacerbation	Doxycycline: tolerates Minocycline: Erythematous maculopapular rash	Mild	Minocycline: Positive	Minocycline: Desensitized	Successful
H	17F	CF	Doxycycline: rash,	Mod.	Doxycycline:	Doxycycline:	Successful

		exacerbation	pruritus, knee pain Tigecycline: possible, but unlikely culprit in DRESS, starting on day 14 Tolerates minocycline		Negative Tigecycline: Negative	Graded Challenge Tigecycline: Graded Challenge	
I	13M	MRSA cellulitis	Doxycycline: pruritic, erythematous rash on arms and buttocks, mild dyspnea	Mod.	Doxycycline: Negative	Doxycycline: Graded Challenge	Successful
J	17M	MRSA cellulitis	Doxycycline: self-limited urticaria on day 5 of therapy	Mild	Doxycycline: Negative Minocycline: Positive	Pending	

Table I: Patient Characteristics

Severity based upon Brown Classification Criteria: Mild (skin and subcutaneous involvement only); Moderate (features suggestive of respiratory, cardiovascular or gastrointestinal involvement; Severe (hypoxia, hypotension, or neurologic involvement) Patient F was successfully desensitized to minocycline and tigecycline twice. CF: Cystic Fibrosis; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; Mod.: Moderate

Doxycycline		Minocycline		Tetracycline	
Method	Concentration	Method	Concentration	Method	Concentration
SPT	10 mg/ml	SPT	0.2 mg/ml	SPT	1 mg/ml
ID	0.001 mg/ml	ID	0.002 mg/ml	ID	0.01 mg/ml
	0.0001 mg/ml		0.0002 mg/ml		0.1 mg/ml

Table II. Doxycycline, Minocycline and Tigecycline skin testing regimens. Three control patients were tested for doxycycline, 2 for minocycline and 1 for tigecycline. SPT: Skin Prick Test, ID: Intradermal

Step	Dose (mg)	Time (min)	Cumulative Dose (mg)
1	0.00001	30	0.00001
2	0.0001	30	0.00011
3	0.001	30	0.00111
4	0.01	30	0.01111
5	0.1	30	0.11111
6	1	30	1
7	2	30	3
8	4	30	7
9	8	30	15
10	12	30	27
11	25	30	52
12	50	30	102

Table III. Protocol for Desensitization to Oral Doxycycline, goal 100 mg every 12 hours. Low starting dose for the desensitization was based on the skin test concentration that the patient reacted to.

Step	Dose (mg)	Time (min)	Cumulative Dose (mg)
1	0.01 mg	15	0.01
2	0.02 mg	15	0.03
3	0.04 mg	15	0.07
4	0.08 mg	15	0.15
5	0.16 mg	15	0.31
6	0.32 mg	15	0.63
7	0.64 mg	15	1.27
8	1.28 mg	15	2.55
9	2.56 mg	15	5.11
10	5.0 mg	15	10.11
11	10.0 mg	15	20.11
12	20 mg	15	40.11
13	40 mg	15	80.11
14	60 mg	15	140

Table IV. Protocol for Desensitization to Oral Minocycline, goal 100 mg every 12 hours

	Volume of Diluent (mL)	Drug Concentration (mg/mL)		Total Drug to be Injected into Each Bottle (mg)	
Solution 1	250	0.002		0.50	
Solution 2	250	0.020		5.0	
Solution 3	250	0.198		49.607	
Step	Solution	Rate (mL/h)	Time (min)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2	15	0.0010	0.0010
2	1	5	15	0.0025	0.0035
3	1	10	15	0.0050	0.0085
4	1	20	15	0.0100	0.0185
5	2	5	15	0.0250	0.0435
6	2	10	15	0.0500	0.0935
7	2	20	15	0.1000	0.1935
8	2	40	15	0.2000	0.3935
9	3	10	15	0.4961	0.8896
10	3	20	15	0.9921	1.8817
11	3	40	15	1.9843	3.8660
12	3	75	186	46.1340	50.0000
Total infusion time			351		

Table V: Intravenous Desensitization Protocol for Tigecycline, goal 50 mg every 12 hours