

GENERAL GYNECOLOGY

Management of *Trichomonas vaginalis* in women with suspected metronidazole hypersensitivity

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BACKGROUND/OBJECTIVE: Standard treatment for *Trichomonas vaginalis* is metronidazole or tinidazole. Hypersensitivity to these drugs has been documented but is poorly understood. Desensitization is an option described in limited reports of women with hypersensitivity to nitroimidazoles. The purpose of this analysis is to improve documentation of management for trichomonas infections among women with metronidazole hypersensitivity.

STUDY DESIGN: Clinicians who consulted Centers for Disease Control and Prevention concerning patients with suspected hypersensitivity to metronidazole were provided with treatment options and asked to report outcomes.

RESULTS: From September 2003–September 2006, complete information was obtained for 59 women. The most common reactions were urticaria (47%) and facial edema (11%). Fifteen of these women (25.4%) were treated with metronidazole desensitization and all had eradication of their infection. Seventeen women (28.8%) were treated with alternative intravaginal drugs, which were less successful; 5 of 17 infections (29.4%) were eradicated.

CONCLUSION: Metronidazole desensitization was effective in the management of women with nitroimidazole hypersensitivity.

Key words: desensitization, hypersensitivity, metronidazole, tinidazole, trichomonas

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Trichomonas vaginalis is the most common nonviral sexually transmitted disease in the United States, with an estimated 7 million new infections occurring annually.¹ A recent national survey found an estimated overall prevalence of 3.1% in women in the United States, with a prevalence of 13.5% in non-Hispanic black women, compared with 1.2% in non-Hispanic white women.² *T vaginalis* is spread from person to person through sexual intercourse. The parasite resides in the female lower genital tract, including the vagina, cervix, urethra, bladder, and Bartholin's

and Skene's glands.³ Trichomonas infections vary in severity from being asymptomatic (50% of infections in women) to causing an acute inflammatory vaginitis.^{3,4} Symptoms associated with trichomoniasis in women include yellow/green vaginal discharge, vulvar itching, vaginal erythema, and abdominal pain.^{3,5} *T vaginalis* has been associated with human immunodeficiency virus acquisition and adverse birth outcomes (eg, premature rupture of the membranes, preterm delivery, and low birthweight).^{6,7}

Nitroimidazoles are the recommended treatment for trichomonas in-

fection. There are 2 drugs in this class approved by the U.S. Food and Drug Administration for treatment of trichomoniasis: metronidazole and tinidazole. The recommended treatment for trichomonas infection is a single 2-g oral dose with either metronidazole or tinidazole.⁸ However, adverse reactions to metronidazole may occur, including immediate-type hypersensitivity responses such as flushing, urticaria, fever, angioedema, and anaphylactic shock.⁹ Because metronidazole and tinidazole have similar chemical structures, persons allergic to metronidazole may also react to tinidazole, a possibility supported by case reports.^{10,11}

There is little documentation on metronidazole hypersensitivity in women infected with *T vaginalis*, and the frequency and severity of these reactions is mostly anecdotal. Consequently, as with many aspects of trichomoniasis,¹² only a few alternatives to the standard treatment recommendations for women with nitroimidazole hypersensitivity reactions have been published. One of these is metronidazole desensitization, which can be delivered by either intravenous (IV) or oral routes; however, the docu-

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TABLE 1
Intravenous and oral incremental dosing protocols

Step	Intravenous ^a			Oral ^b		
	Dose (mg)	Metronidazole concentration	Volume (mL)	Dose (mg)	Metronidazole concentration	Volume (mL)
1	0.005 ^c	0.005 mg/mL	1.0	0.0025	0.025 mg/mL	0.1
2	0.015	0.005 mg/mL	3.0	0.025	0.025 mg/mL	1.0
3	0.05	0.05 mg/mL	1.0	0.25	0.25 mg/mL	1.0
4	0.15	0.05 mg/mL	3.0	2.5	2.5 mg/mL	1.0
5	0.5	0.5 mg/mL	1.0	25.0	2.5 mg/mL	10.0
6	1.5	0.5 mg/mL	3.0	250.0	250 mg	Tablet
7	5.0	5.0 mg/mL	1.0	750.0	7500 mg	Tablets
8	15.0	5.0 mg/mL	3.0	1000.0	1000 mg	Tablets
9	30.0	5.0 mg/mL	6.0	—	—	—
10	60.0	5.0 mg/mL	12.0	—	—	—
11	125.0	5.0 mg/mL	25.0	—	—	—
12	250.0 ^d	250 mg orally	Tablet	—	—	—
13	500.0	500 mg orally	Tablets	—	—	—
14	2000.0	2000 mg orally	Tablets	—	—	—

^a Pearlman et al.¹³

^b Kurohara et al.¹⁴ Doses are given over the course of 1 day.

^c Intravenous increments are administered in 15-20 minute intervals.

^d Oral doses are given 1 hour apart.

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mented evidence for efficacy of metronidazole desensitization is limited to a few case reports.^{13,14}

There are also a few alternatives to a nitroimidazole compound available, including furazolidone, paromomycin sulfate, and Betadine douche or Betadine suppositories, all of which have high failure rates.¹⁵ A limitation of these alternative regimens is that they must be administered intravaginally. Intravaginal treatments may not be as effective as oral treatments because they may not reach all of the sites in which the trichomonads reside, including the Bartholin's and Skene's glands.^{3,16} Although symptoms may resolve initially with intravaginal treatment, failure to eradicate the parasites from sequestered sites may result in clinical failure.

The Division of STD Prevention and the Division of Parasitic Diseases at the Centers for Disease Control and Prevention (CDC) serve as sources of consultation on the management of women with suspected hypersensitivity to metronidazole. In response to an increase in the

number providers seeking assistance in treatment of women with reported metronidazole hypersensitivity, a surveillance system was initiated in September 2003 to monitor clinical management following the consultation and to determine outcomes of the various treatment regimens that were utilized. The purpose of this analysis was to investigate the effectiveness of the metronidazole desensitization protocols as well as the alternatives to nitroimidazoles for the treatment of trichomonas infection in women with suspected metronidazole hypersensitivity.

MATERIALS AND METHODS

Since September 2003, all providers who contacted the CDC's Division of STD Prevention or Division of Parasitic Diseases seeking consultation for treatment options for trichomonas in women with hypersensitivity to metronidazole were asked to provide the following patient information: age, pregnancy status, hypersensitivity reaction, treatment that

caused the reaction, and whether the reaction was directly observed by the provider. Various treatment options were discussed including metronidazole desensitization and intravaginal furazolidone; this information was sent to the provider upon request (Table 1).^{13,14} The choice of treatment was determined by the provider, although we strongly recommended using one of the desensitization protocols. The use of any alternative therapies utilized by the providers were not standardized in dose or duration. The data were collected as an evaluation of our standard service activities and no patient identifiers were collected.

Beginning in January 2005, additional information was requested following treatment: treatment regimen, oral or IV metronidazole desensitization or an alternative drug; whether adverse effects occurred during the therapy; and documentation of a microbiologic or clinical cure. Follow-up information from providers who requested consultation prior to January 2005 was obtained retrospectively by telephone or fax. If the provider

did not return the follow-up form within 2 months after consultation, telephone contact was initiated.

Treatment outcome was determined on the basis of both the provider's clinical impression and the available microbiologic tests results. A microbiologic cure was defined as a negative trichomonas culture. A negative wet mount, in addition to a complete resolution of signs and symptoms, was defined as a suspected microbiologic cure. If no test of cure was performed, the treatment outcome was based on the provider's clinical impression. A suspected clinical cure was defined as complete resolution of signs and symptoms of trichomonas infection.

We analyzed the data from Sept. 1, 2003-Sept. 30, 2006, to determine the most effective treatment for trichomonas infection in women with metronidazole hypersensitivity. We stratified women by demographic and clinical characteristics, including age (18-24, 25-40, and older than 40 years of age) and weight (100 or less, 101-150, 151-200, and more than 200 pounds). We compared the use and effectiveness of the 2 desensitization protocols and the intra-vaginal treatments with alternative drugs.

RESULTS

Provider characteristics

From September 1, 2003-September 30, 2006, 127 providers requested consultation in managing women with trichomonas infection and suspected metronidazole hypersensitivity. The women were seen by a variety of providers in a variety of clinical settings and diverse geographic areas (Table 2). Fifty percent of providers requesting consultation had witnessed a hypersensitivity reaction. Fifty-nine of the 127 providers (47%) returned follow-up information (Table 2). Providers were more likely to return follow-up information on women in whom they had directly observed the suspected hypersensitivity reaction than from women who had self-reported or were referred after experiencing a hypersensitivity reaction (59% vs 35%).

TABLE 2

Characteristics of providers who requested consultation on management of *Trichomonas vaginalis* and possible metronidazole allergy and characteristics of their patients, 2003-2006

	Initial call		Follow-up ^a	
	n	(%) ^b	n	n/N (%)
Total	127	100.0	59	46.5
Provider characteristics				
Provider				
Physician	56	44.1	26	46.4
Nurse practitioner	28	22.0	15	53.6
Nurse	6	4.7	2	33.3
Physician's assistant	5	3.9	3	60.0
Other	32	25.2	13	40.6
Type of facility				
Corrections	4	3.1	3	75.0
Hospital	16	12.6	6	37.5
Infectious disease	5	3.9	3	60.0
Obstetrics/gynecology	30	23.6	10	33.3
Private practice	38	29.9	22	57.9
Public clinic	26	20.5	11	42.3
Other	8	6.3	4	50.0
Region ^c				
Midwest	28	22.0	11	39.3
Northeast	10	7.9	7	70.0
South	69	54.3	30	43.5
West	19	15.0	10	52.6
Referral ^d				
Yes	63	49.6	22	34.9
No	64	50.4	37	59.1
Patient characteristics				
Reported hypersensitive reactions ^e				
Anaphylaxis	11	6.9	2	18.2
Erythematous rash	10	6.3	7	70.0
Facial edema	18	11.3	8	44.4
Gastrointestinal intolerance	9	5.7	5	55.6
Pruritus	16	10.0	10	62.5
Urticaria	74	46.5	31	41.9
Other ^f	21	13.2	9	42.9

^a Follow-up refers to whether a provider returned any follow-up information on the patient after assistance from the CDC.

^b Percentages may not always add to 100, based on missing data.

^c Based on U.S. census regions.

^d Woman self-reported hypersensitivity or was referred to provider after initial hypersensitive reaction.

^e Can have more than 1 reported reaction.

^f Other includes flushing, shortness of breath, general swelling, dizziness, Stevens-Johnson syndrome, and seizure.

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Patient characteristics

The average age of the 127 women with suspected metronidazole hypersensitivity was 36 years (range, 18-73 years). Twenty-seven women (21%) were between the ages of 18 and 25 years, 54 (43%) were aged 26-40 years, and 38 (29%) of the women were older than 40 years old. Age was missing for 8 of the women. The average weight of the women was 171 pounds (range, 95-302 pounds). Thirty-one (24%) woman weighed less than 150 pounds, 47 (37%) weighed between 151 and 200 pounds, and 18 (14%) weighed more than 200 pounds. Weight data were missing for 31 women. Thirteen (10%) of the women were pregnant at the time of consultation.

The most commonly reported reaction to metronidazole was urticaria (47%). Typically, we did not equate gastrointestinal (GI) intolerance with hypersensitivity, but the 9 women who experienced GI intolerance to metronidazole (5.7%) also experienced at least one other concurrent hypersensitivity reaction.

Sixty-four (50%) of the 127 women with suspected hypersensitive reactions were directly observed by their provider. Providers directly observed a variety of suspected hypersensitivity reactions ($n = 82$) in the women: 39 urticaria reactions (48%), 13 pruritic reactions (16%), 7 facial edema reactions (9%), 6 GI intolerance (7%), 2 anaphylactic reactions (2%), 7 erythematous rashes (9%), and 8 other types of reactions (10%).

Women with self-reported hypersensitivity or who were referred to their provider for treatment after experiencing suspected hypersensitivity reported the following hypersensitivity reactions: 35 urticaria reactions (45%), 3 pruritic reactions (4%), 11 facial edema reactions (14%), 3 GI reactions (4%), 9 anaphylactic reactions (12%), 3 erythematous rashes (4%), and 13 other types of reactions (17%).

Response to metronidazole desensitization

Fifty-nine women had follow-up information available; 41 women were treated

following consultation, and 18 women were not treated (Figure). Reasons that were provided for not receiving treatment included initial treatment cure, being transferred or released from a correctional facility, the cost associated with the desensitization procedure, or the lack of resources to monitor the patient during the desensitization procedure.

Fifteen of the 41 women (37%) were treated using either the oral (8 women) or IV (7 women) metronidazole desensitization regimens (Figure). All fifteen of these women (100%) were cured (3 microbiologic, 9 suspected microbiologic, 3 clinical) with minimal to no side effects. One woman who received oral metronidazole desensitization experienced a pruritic rash on the final day and was administered steroids with resolution of the rash. One woman who received IV metronidazole desensitization experienced mild urticaria and pruritus 45 minutes following the final 2-g dose and was managed with Benadryl and displayed prompt resolution of symptoms.

Alternative treatments

Of the 41 women who received treatment after consultation, 26 women (64%) were not treated using either of the metronidazole desensitization regimens (Figure). Upon further discussion, some providers reported that 9 of the 26 women (35%) had no clear history of hypersensitivity and were treated with a standard metronidazole or tinidazole regimen. None of these women displayed a hypersensitive reaction during treatment, and 6 of 7 (86%) cured (6 suspected) their trichomonas infection. Seventeen of the 26 women (65%) received intravaginal treatment with an alternative drug. The alternative treatments include Betadine douche (6 women), intravaginal paromomycin (5 women), intravaginal clotrimazole (3 women), intravaginal furazolidone (2 women), and intravaginal acetarsol (1 woman). These alternative treatments were not standardized in either the dose or the duration of treatment, except for furazolidone, and were used at the discretion of the provider.

Treatment outcome was available for 12 of these 17 women. A suspected microbiologic cure and resolution of symptoms was documented in 3 of the 4 women who used Betadine douche, 1 of the 3 women who used intravaginal clotrimazole, and 1 of the 4 women who used intravaginal paromomycin. The 1 woman whose trichomonas infection was eradicated using paromomycin experienced vaginal ulceration. Neither woman who received furazolidone showed any treatment response. Subsequently 1 of these women had a suspected clinical cure of her trichomonas infection using a Betadine douche.

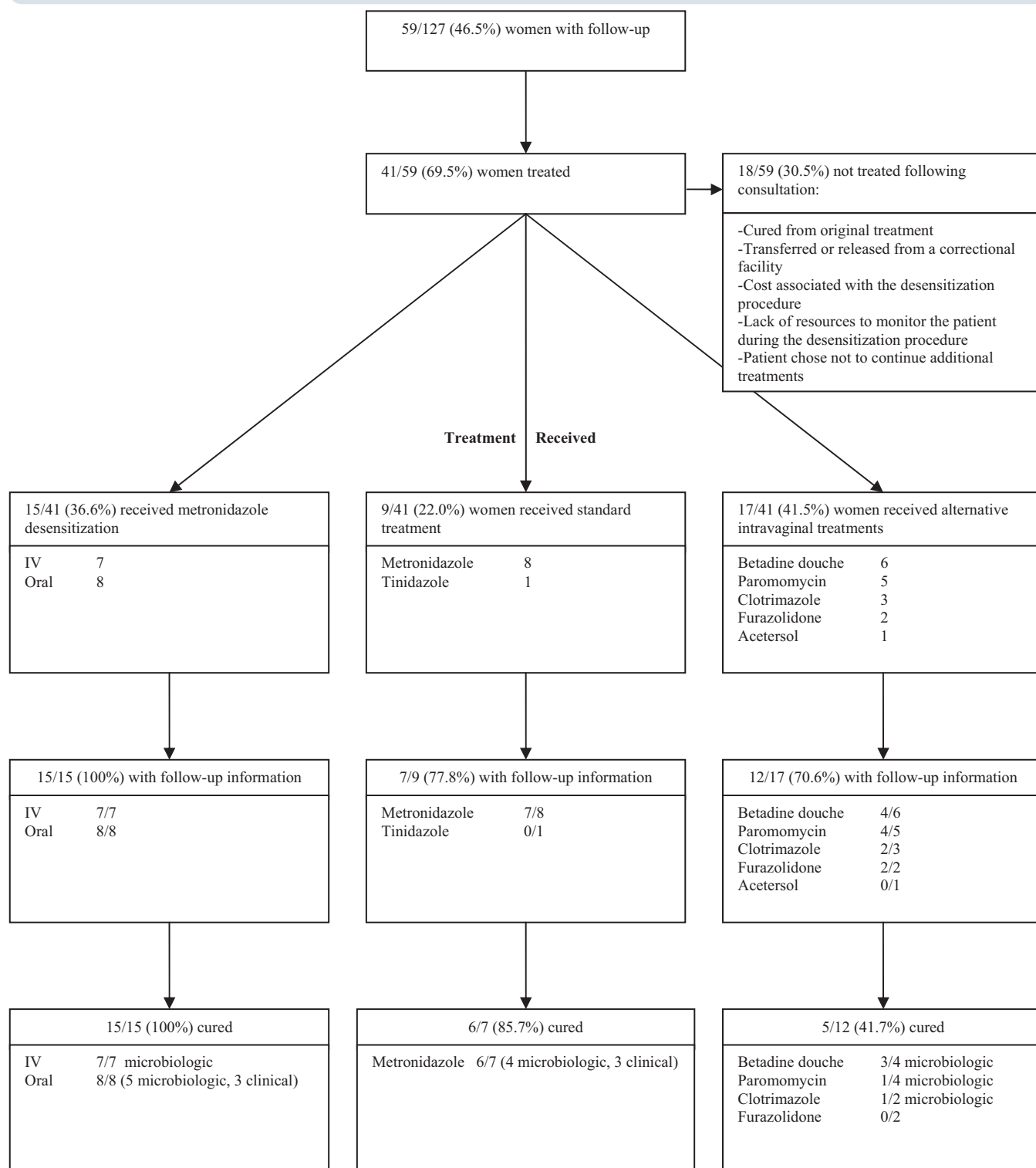
COMMENT

This evaluation sought to better document the effectiveness of treatment options used for management of women with metronidazole hypersensitivity. There are few published alternatives for treatment of trichomonas infection, and there have been only a few case reports of effective metronidazole desensitization for women with metronidazole hypersensitivity.^{13,14} Intravaginal alternatives have not been well studied and can be associated with adverse reactions.^{15,17-20} Thus, to evaluate the quality of our treatment recommendations for metronidazole-hypersensitive women with trichomoniasis, we collected data on treatment outcomes from their health providers. We found that the oral and IV metronidazole desensitization regimens were 100% effective (15 of 15) in the management of trichomonas infection in women with nitroimidazole hypersensitivity. Nitroimidazole desensitization was associated with minor adverse reactions in 2 women but was effectively managed with antihistamines and steroids, similar to the limited adverse reaction previously described in the oral desensitization case study.¹³

Many of the providers who sought consultation chose not to utilize the desensitization regimens. The providers' decisions to use alternative therapies included the cost of IV desensitization, lack of facilities to monitor desensitization, and the inability to obtain approval from the supervisory physician to autho-

FIGURE

Flow chart of women for whom follow-up information was provided



Final treatment outcome information was available for 34 of the women (58%). Microbiologic cure indicates that women were negative for *T. vaginalis* by wet mount or culture on the follow-up visit after treatment. Clinical cure indicates that women had no symptoms of trichomoniasis at the follow-up visit.

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alize the procedure. Treatment effectiveness was achieved in only 5 of 12 women (42%) who received alternative intravaginal treatment regimens, all of whom had suspected microbiologic cure. Of these, 3 of the 4 of the women treated with Betadine douches were cleared of infection. However, no standard dose or duration of the topical Betadine was used. Previous reports documented some effectiveness of Betadine douche or povidone-iodine pessaries.^{15,21} There is also evidence that Betadine may be effective against *T vaginalis* in vitro (W. E. Secor, unpublished data).

In this evaluation, intravaginal paromomycin was effective in eradicating trichomonas infection in only 1 of 4 women but was associated with vaginal ulceration, consistent with the adverse reaction described in a previous case report.²² Paromomycin is an aminocyclitol antibiotic that is applied intravaginally because it is not absorbed by the gastrointestinal tract. Nyirjesy et al²² reported that using paromomycin intravaginally for 2 weeks in women with metronidazole hypersensitivity was effective in 6 of 9 women, although 1 woman experienced a relapse 2 weeks after treatment.

Only 1 of the 3 women treated with clotrimazole demonstrated suspected microbiologic cure of her trichomonas infection, which is similar to other studies.^{19,23,24} A recent multicenter trial documented a 11% success rate in women treated with clotrimazole.²³

Neither furazolidone (2 patients) nor acetarsol (1 patient) appeared effective for treatment of trichomoniasis in women with metronidazole hypersensitivity in the current evaluation. Furazolidone is a nitrofurantoin and a potent monoamine oxidase inhibitor, and its in vitro effectiveness against *T vaginalis* has been documented.^{25,26} Our findings were inconsistent with another study in which treatment with intravaginal furazolidone demonstrated clearance of trichomonas infection within 72 hours in 45 of 48 women, with only 3 patients experiencing further symptoms in the following 1-3 months.²⁷ Acetarsol is an arsenical compound and has demonstrated effectiveness as well as treatment

failure.^{20,28} Acetarsol has been associated with vaginal irritation and a generalized rash.

A limitation to this evaluation is the inconsistent method used for the diagnostic testing to define cure. This evaluation had to rely heavily on what diagnostic methods clinicians had available. Wet mount has a sensitivity of 40-80% and is the most commonly used method of diagnosis in the clinic setting. It relies on visual detection of viable organisms with characteristic motility, size, and morphology.²⁹ Few providers had the availability to perform culture. Currently culture is the gold standard for diagnosis because of its higher sensitivity (up to 95%).²⁹ Only 3 women's cures were based on a negative culture. It is possible that as many as 50% of the women with apparent microbiologic cures may not have been completely cleared of infection because of the insensitivity of wet mount to define treatment outcome.

We were unable to obtain information on time between treatment and follow-up. Although we recommended clinical assessment occur 3 weeks following treatment, few clinicians provided this information. If the assessment of cure was performed too early, it may be that some women with apparent microbiologic cure may have had a residual infection. Nevertheless, the incremental dosing protocols consistently achieved clinical and/or apparent microbiologic cure in a manner that was safe for women with suspected hypersensitivity to metronidazole.

This evaluation most likely underrepresents the number of women experiencing metronidazole hypersensitivity and is limited by its passive inclusion strategy. The evaluation began as a response to consultation requests from providers caring for women with suspected metronidazole hypersensitivity. Because of a small sample size of women in this evaluation, the success rate may not be generalizable to a larger population. However, this evaluation appears to be the largest case series that examines the treatment options for women with suspected metronidazole hypersensitivity. In addition, the success of the desensiti-

zation for women shows that it is a safer method for treating women with hypersensitivity to metronidazole.

Overall, this evaluation confirmed that the oral and IV metronidazole incremental dosing protocols are effective in the management of trichomonas infection in women with hypersensitivity to nitroimidazoles. Although treatment with alternative drugs had some success, topical therapies appear less effective than metronidazole desensitization. Nevertheless, the development of new, nonnitroimidazole oral alternatives for the management of women with trichomoniasis and metronidazole hypersensitivity remains a need for the effective management of the disease. ■

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