

Trichomoniasis: Challenges to Appropriate Management

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***Trichomonas vaginalis* infection is a common cause of vaginal irritation in women and is the most common nonviral sexually transmitted disease in the world. It has been associated with serious sequelae, the most notable of which are prematurity, low birth weight, and increases in human immunodeficiency virus transmission. We review advances in diagnosis and treatment and the current controversies regarding management.**

Trichomoniasis is the most common nonviral sexually transmitted disease (STD) in the world [1]. It is estimated to affect 5 million women in the United States each year [2]. A recent population-based study of young adults in the United States found an overall trichomoniasis prevalence of 2.3%, with a rate of 2.8% among women and a rate of 1.7% among men [3]. As has been seen in other studies, there was racial disparity in trichomoniasis prevalence, with the highest rates reported among black women. In the United States, trichomoniasis prevalence among women attending STD clinics and antenatal clinics has been reported to be as high as 28% and 34%, respectively [4, 5]. Among men attending US STD clinics, trichomoniasis prevalence has been reported to be 13%–17% [6, 7].

Interest in this protozoal STD has increased as the potential complications of the infection have become clearer. trichomoniasis has long been recognized as a common cause of vaginal itching, odor, and discharge in women and of urethritis in men, but data now link trichomoniasis to premature rupture of membranes, premature delivery, low birth weight, stillbirth, neonatal death, HIV transmission, pelvic inflammatory disease,

and chronic prostatitis [8–16]. Limited data also link trichomoniasis to an increased risk for cervical dysplasia and neoplasia and male infertility [17, 18]. In this article, we review new developments in diagnostics and therapeutics and discuss continuing controversies in the management of vaginal trichomoniasis.

DIAGNOSIS

Even with increasing recognition of trichomoniasis-related morbidity, the poor sensitivity of wet preparation (60%–70%) and the incubator and time requirements of culture have hindered control of this common STD [19]. The reference standard for trichomoniasis diagnosis continues to be culture. Commonly used *Trichomonas vaginalis* (TV) media include Diamond's, Trichosel, and InPouch TV (BioMed Diagnostics). The InPouch TV test has media prepackaged in plastic pouches that are directly inoculated. The pouches can be evaluated daily under the microscope during incubation.

New methods of diagnosis, such as PCR assays, have demonstrated high sensitivity and specificity and are aiding epidemiologic evaluations of disease prevalence, as well as studies investigating the morbidity of disease [5, 20, 21]. For women, PCR assay of a vaginal swab sample appears to be superior to PCR assay of a urine sample, in part because of the presence of PCR inhibitors in urine [5]. TV PCR results should be negative by 2 weeks after completion of successful therapy [22]. Unfortunately, TV PCR has not yet been cleared by the

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US Food and Drug Administration (FDA), and expense and availability may hinder its widespread use.

Two FDA-approved, point-of-care tests for vaginal trichomoniasis are now available and include the OSOM Trichomonas Rapid Test (Genzyme Diagnostics), an immunochromatographic capillary-flow dipstick technology, and the Affirm VP III (Becton Dickinson), a nucleic acid probe test that evaluates for TV, *Gardnerella vaginalis*, and *Candida albicans*. These tests are both performed on vaginal secretions and have a sensitivity >83% and a specificity >97% [23–25]. The results of the OSOM Trichomonas Rapid Test are available in ~10 min, and the results of the Affirm VP III are available within 45 min. These tests tend to be more sensitive than vaginal wet preparation and may greatly assist physicians in the accurate and timely diagnosis of trichomoniasis.

The use of Papanicolaou smear in trichomoniasis diagnosis remains controversial. In general, it is not recommended as a screening test, because of its low sensitivity and the delay in obtaining results. Some experts also feel that the specificity is highly operator dependant and discourage the diagnosis of trichomoniasis made solely on the basis of a Papanicolaou smear result. However, recent data suggest that the positive predictive value of this test is acceptable for a diagnosis of trichomoniasis when it is found incidentally on Papanicolaou smear. In 2000, a meta-analysis by Wiese et al. [19] found a sensitivity of 57% and a specificity of 97%. A recent study of 203 women evaluating the reliability of liquid-based Papanicolaou smear in comparison with TV culture showed an overall sensitivity, specificity, positive predictive value, and negative predictive value of 61.4%, 99.4%, 96.4%, and 90.8%, respectively [26]. However, in low-prevalence settings, the possibility of a false-positive Papanicolaou smear, OSOM Trichomonas Rapid Test, or Affirm VP III result increases, and clinicians should consider performing a wet preparation or TV culture to confirm the diagnosis.

TREATMENT

For several decades, the effective treatment of trichomoniasis in the United States has relied solely on the use of metronidazole. Tinidazole, another 5-nitroimidazole, was introduced for the treatment of trichomoniasis in 1969 and has been available outside the United States for several decades. The FDA recently approved tinidazole for use in the treatment of vaginal trichomoniasis. The best use of this agent, the appropriate management of disease during pregnancy, and the management of disease that is unresponsive to metronidazole remain issues of controversy in the management of vaginal trichomoniasis.

Tinidazole is now available in the United States, under the trade name Tindamax (Mission Pharmacal), in a 250-mg tablet and a 500-mg tablet and should be administered with food. Common adverse effects include nausea, vomiting, constipation, cramping, and metallic taste. Other adverse effects that can occur

include peripheral neuropathy, seizures, fatigue, dizziness, headache, and leukopenia. Several features distinguish tinidazole from metronidazole and suggest a role for this medication in the treatment of metronidazole-refractory trichomoniasis. Tinidazole has a half-life of ~12.5 h, compared with a half-life of 7.3 h for metronidazole [27]. In addition, serum and genitourinary tract levels of tinidazole have been reported to be 1.4- to 2-fold higher than those of metronidazole [28, 29].

The efficacy of tinidazole in the treatment of uncomplicated vaginal trichomoniasis is well established. The largest trial of tinidazole treatment (2-g single oral dose) for trichomoniasis in women was a multicenter, open-label trial demonstrating parasitologic cure, as assessed by wet preparation, in 818 (95%) of 859 women [30]. Randomized controlled trials comparing tinidazole (2-g single oral dose) and either metronidazole (2-g single oral dose) or short-course metronidazole have demonstrated parasitologic cure rates of 86%–100% for tinidazole [31–37]. In these trials, the efficacy of tinidazole has been equivalent or superior to that of metronidazole. In a Cochrane database meta-analysis of randomized trials comparing short-course therapy with tinidazole and short-course therapy with metronidazole for trichomoniasis, metronidazole had significantly higher rates of parasitologic failure (relative risk [RR], 3.2), clinical failure (RR, 3.8), and adverse effects (RR, 1.65) [38].

The FDA has approved tinidazole (2-g single oral dose) for the treatment of trichomoniasis in men and women. However, currently, cost issues would favor the use of metronidazole unless adverse effects, availability, or treatment failure with metronidazole becomes an issue. There are no data to suggest that tinidazole would be safe to use in a patient with metronidazole allergy. These drugs are both nitroimidazoles, and allergic cross-reactivity remains undefined. The efficacy of tinidazole in the treatment of metronidazole-resistant TV infection is encouraging, but the timing of the switch to tinidazole therapy and the dose required remain undefined.

Metronidazole-resistant TV. Clinical resistance to metronidazole, defined by therapeutic failure, has been reported since 1962. In 1991, Lossick and Kent [39] estimated that marginal resistance occurred in 1 of every 50–75 cases, low to moderate resistance occurred in 1 of 200–400 cases, and very-high-level resistance occurred in 1 of 2000–3000 cases. Small surveillance studies conducted in Atlanta, Georgia, and in Spain have been published since that time, demonstrating rates of low-level metronidazole resistance (minimal lethal concentration [MLC], ≥ 50 $\mu\text{g/mL}$) of 2.2%–2.5% [40, 41]. Follow-up was available in only 1 of 2 cases identified in Atlanta, and that patient was cured after being administered metronidazole (2 g) as a single oral dose. These studies suggest that metronidazole continues to have good overall clinical efficacy. However, when metronidazole-resistant TV infection occurs, it is a therapeutic challenge and is associated with significant patient suffering.

Antibiotic susceptibility testing for TV is not standardized.

However, most studies assess the MLC of metronidazole or other imidazoles over 48 h under aerobic and anaerobic incubation conditions [40]. Although aerobic metronidazole MLCs of $>200\text{ }\mu\text{g/mL}$ correspond closely to clinical metronidazole treatment failure, there can be significant variability in clinical response to metronidazole therapy when aerobic MLCs range from 50 to $200\text{ }\mu\text{g/mL}$, and clinical resistance has even been reported in patients with metronidazole MLCs of $12.5\text{ }\mu\text{g/mL}$ [42, 43]. In practice, the imperfect correlation of metronidazole MLCs with clinical response and the limited access to TV culture and susceptibility testing favor the determination of resistance based on patient adherence and clinical response to therapy [44].

Many isolates with clinical resistance to standard treatment regimens and with evidence of metronidazole resistance on aerobic resistance testing respond to higher doses of metronidazole (87%) [42]. Metronidazole doses as high as 1 g 3 times daily coupled with intravaginal metronidazole (500 mg daily for 14 days) (total dose, 49 g) have been successfully used for refractory cases with metronidazole aerobic MLCs as high as $1000\text{ }\mu\text{g/mL}$. At such high doses, metronidazole treatment-limiting toxicity can include nausea, vomiting, peripheral neuropathy, neutropenia, and pancreatitis. For this reason, alternative therapies are needed.

In vitro data support the likelihood of improved efficacy with tinidazole in cases of metronidazole treatment failure [45]. In an evaluation of 104 clinical isolates from patients with metronidazole treatment failure, the mean aerobic MLC for tinidazole was $\sim 1014.9\text{ }\mu\text{mol/L}$, compared with $2618\text{ }\mu\text{mol/L}$ for metronidazole. Sixty percent of isolates had a lower MLC to tinidazole than to metronidazole. In addition, serum and genitourinary tract drug levels of tinidazole are 1.5- to 2-fold higher than those of metronidazole in men receiving 500 mg of each medication 3 times daily and 1.4- to 1.8-fold higher than those of metronidazole in women receiving 400 mg of metronidazole 3 times daily or 500 mg of tinidazole twice daily [29].

Tinidazole (2-g single dose) has been shown to have efficacy in a limited number of cases of documented TV after divided-dose metronidazole therapy of unspecified length (2 of 2 cases cured) and standard 7-day metronidazole therapy (13 of 14 cases cured) (table 1) [31, 35]. Although the incidence of high-level metronidazole resistance appears to be low, several case series have been published since 2000 documenting cases of metronidazole treatment failure, with the largest case series study reporting on 24 cases [44]. Several of these reports have documented the response to oral tinidazole with or without intravaginal tinidazole, with dosing regimens ranging from 2 g of tinidazole administered orally daily for 2 days to 1 g of tinidazole administered orally 3 times daily with 500 mg administered intravaginally 3 times daily for 14 days [44, 49]. In patients who experience clinical failure with metronidazole, tinidazole at a dose of 1 g administered twice daily orally with

500 mg administered intravaginally twice daily or 1 g administered orally 3 times daily with 500 mg administered intravaginally 3 times daily for 14 days resulted in a parasitologic cure in 8 of 10 patients for whom findings were reported (Presutti Laboratories, personal communication).

Tolerance of high-dose tinidazole is good, with generally mild adverse effects [44]. Adverse effects were closely monitored in the Presutti Laboratories tinidazole compassionate availability program, with 6 of 9 patients reporting metallic taste, 4 of 9 reporting nausea, 2 of 9 reporting yeast infection, and 1 of 9 reporting fatigue, thirst, urinary frequency, watery discharge, vaginal bleeding, or vaginal itching (Presutti Laboratories, personal communication). The estimated maximum and minimum serum concentrations of tinidazole (1 g orally twice daily with 500 mg intravaginally for 14 days) are $53.4\text{ }\mu\text{g/mL}$ and $28.9\text{ }\mu\text{g/mL}$, respectively. Limited data collected in the compassionate availability program demonstrated levels within this range ($30.3\text{--}33.8\text{ }\mu\text{g/mL}$ at 6.5 and 8.25 h after a dose) and showed no evidence of tinidazole accumulation ($19.6\text{--}24.1\text{ }\mu\text{g/mL}$ at 15.1–15.25 h after the last dose).

Unfortunately, there are no data to guide the timing or optimal dose of tinidazole in the case of metronidazole treatment failure. If treatment failure occurs with metronidazole (2-g single dose) and reinfection is excluded, the patient can be treated with metronidazole (500 mg orally twice daily for 7 days) or tinidazole (2-g single dose) (figure 1). Patients for whom either of these therapies fail should be treated with metronidazole or tinidazole (2 g daily for 5 days). Patients who experience treatment failure at this dose should be managed in consultation with an expert. The consultation should include testing of the organism for metronidazole and tinidazole susceptibility. The Centers for Disease Control and Prevention (Division of STD Prevention and Division of Parasitic Diseases) has accumulated experience with testing for and treatment of imidazole-resistant TV infection and can offer valuable consultation for testing and management.

There are in vitro susceptibility data or limited reports of successful therapy for trichomoniasis with intravaginal paromomycin, povidone-iodine, furazolidone, or nonoxynol-9 [55–58]. These agents could be considered in cases of metronidazole-resistant TV infection. However, topically applied agents tend to have limited efficacy. For instance, the efficacy of intravaginal paromomycin in metronidazole-resistant TV has been reported to be 58% [44]. In part, the limited efficacy of topical therapy is thought to be due to sequestered organisms in the perivaginal glands.

Treatment during pregnancy. The treatment of trichomoniasis during pregnancy has been a controversial issue since the introduction of metronidazole. Concerns first emerged regarding the safety of metronidazole in pregnancy as a result of reports of mutagenesis in bacteria and carcinogenesis in rodents. However, these reports have not been confirmed in nu-

Table 1. Tinidazole use in clinically defined metronidazole-resistant *Trichomonas vaginalis* infection.

Reference	No. of patients	Metronidazole aerobic MLC, $\mu\text{g/mL}$	Tinidazole aerobic MLC, $\mu\text{g/mL}$	Dose of tinidazole	Test of cure	Follow-up	Efficacy, no. cured/total treated
Forsgren and Forssman [46]	1	160	80	2 g po single dose; 4 g po single dose	NA	NA	0/1
Voolmann and Boreham [47]	1	400 ^a	12.5–25 ^a	Failure of unspecified therapy, then 2 g po b.i.d. with 500 mg ivg at bedtime for 16 days with 3% acetic acid douches at bedtime for 10 days	Culture, symptoms	6 months	1/1
Lewis et al. [48]	1	500 ^a	...	2 g po daily for 2 days	Wet preparation	7 weeks	1/1
	1	2 g po daily for 2 days	0/1
	1	16 ^a	...	2 g po single dose; 500 mg po b.i.d. for 7 days	0/1
Hamed and Studemeister [49]	1	>1000	>400	2 g po daily for 2 days	Wet preparation	4 months	1/1
Livengood III and Lossick [50]	1	>1000	400	2 g po once; 1 g po b.i.d. for 4 days	0/1
Hager [51]	1	500 mg po t.i.d. for 10 days	Wet preparation	1 month	1/1
	2	500 mg po t.i.d. for 7 days	Wet preparation	1 month	2/2
Dan and Sobel [52]	1	2 g po daily for 14 days	...	3 months	1/1
Lossick and Kent [39]	5	2 g po daily for 7–14 days	5/5
Kanno and Sobel [53]	1	>100 ^a	...	2 g po daily with 1 g ivg daily for 14 days; relapse after 9 months and re-treated with 3 g po daily for 14 days	Symptoms	8 weeks	1/1
Saurina et al. [54]	1	400 to >400	100–400	500 mg po q.i.d. with 500 mg ivg b.i.d. for 14 days	Culture, symptoms	2 months, 5 months	1/1
Sobel et al. [44]	24	32.5 (6.25–200) ^b	...	500 mg po q.i.d. with 500 mg ivg b.i.d. or 1 g po t.i.d. with 500 mg ivg t.i.d. for 14 days	Wet preparation, with or without culture	4–6 weeks	22/24
Nyirjesy et al. [55]	1	200	50	3 g po daily with 1.5 ivg daily for 14 days	0/1
Presutti Laboratories, personal communication	9	200–400 (6.3–1000) ^c	12.5–25 (1.6–400) ^c	1 g po b.i.d. with 500 mg ivg b.i.d. for 14 days	Culture	21–25 days	8/9 ^d
	1	400	50	1 g po t.i.d. with 500 mg ivg t.i.d. for 14 days	Culture	21–25 days	1/1

NOTE. b.i.d., twice daily; ivg, intravaginal; MLC, minimum lethal concentration; NA, not applicable; po, orally; q.i.d., 4 times daily; t.i.d., 3 times daily.

^a Value is a MLC.

^b Median and range for 15 patients.

^c Median and range for 6 patients.

^d One relapse occurred 5 days after the last follow-up.

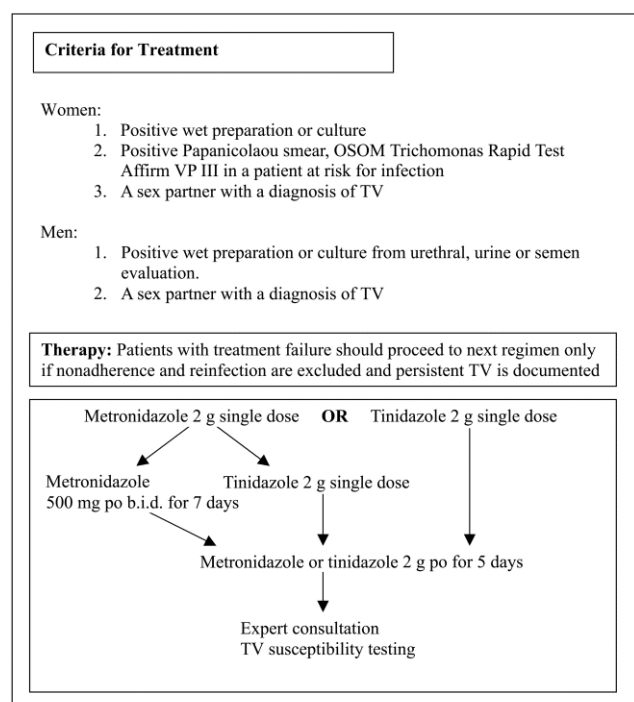


Figure 1. Indications and algorithms for trichomoniasis therapy. b.i.d., twice daily; po, orally; TV, *Trichomonas vaginalis*.

merous cohort studies and meta-analyses [59]. There is no convincing evidence that metronidazole is carcinogenic or teratogenic in humans [60, 61]. Unfortunately, currently there are few data on the use of tinidazole during pregnancy. The drug is classified by the FDA as pregnancy category C. Results of a case-control trial by Czeizel and Rockenbauer [62] did not suggest that there was an increased risk of congenital abnormalities associated with tinidazole use, but the number of women with tinidazole exposure was quite low (10 pregnant

women). Therefore, metronidazole remains the drug of choice for treatment of trichomoniasis in pregnancy.

More recently, as data have accumulated suggesting the role of TV in perinatal morbidity, attention has focused on the use of metronidazole to attempt to decrease TV-associated prematurity and low birth weight. Unfortunately, although earlier small comparative studies of metronidazole treatment versus placebo did not suggest benefit or harm, more recent trials raise concern that treatment may actually increase morbidity, at least in some populations (table 2) [63–66].

An observational study of 880 women compared women with relatively asymptomatic trichomoniasis who did not receive treatment and women who were treated for 7–10 days with metronidazole [63]. There were no significant differences in rates of congenital anomalies, prematurity, or low birth weight between the groups. Similarly, Ross and van Middelkoop [64] conducted a randomized trial of metronidazole therapy (2-g single oral dose) administered to the patient and their partner versus no therapy in pregnant women with trichomoniasis detected by wet preparation. The study included 376 patients; 110 were infected and treated, 115 were infected and not treated, and 151 were not infected. Only 11 patients in the treatment group experienced failure of initial therapy or were reinfected during the study, and 10 were successfully retreated. The majority of untreated infected patients had documented persistent infection during the study. The mean birth weights and gestational age at delivery were not statistically different between the groups.

However, more recently, in a randomized controlled trial of metronidazole treatment of asymptomatic trichomoniasis during pregnancy ($N = 617$), therapy was associated with an increased risk of preterm birth (19% vs. 11%; RR, 1.8; 95% CI, 1.2–2.7) [65]. In this multicenter, placebo-controlled study, treatment was administered as 2-g doses of metronidazole at 48-h intervals at 16–23 weeks' gestation and again between 24

Table 2. Comparative trials of trichomoniasis treatment in pregnancy.

Reference	Study design	Treatment	Low birth weight ^a			Prematurity ^b		
			Control group, no./total (%)	Mtz group, no./total (%)	RR (95% CI)	Control group, no./total (%)	Mtz group, no./total (%)	RR (95% CI)
Morgan [63]	Observational study: treated vs. untreated ($N = 880$)	Mtz, 200 mg po t.i.d. for 7–10 days	53/283 (18.5)	106/597 (17.5)	...	13/283 (4.5)	32/597 (5.3)	...
Ross and van Middelkoop [64]	Randomized trial ($N = 225$)	Mtz, 2 g po single dose	(11)	(12) ^c	... ^c	...
Klebanof et al. [65]	Double-blind, placebo-controlled, randomized trial ($N = 617$)	Mtz, 2 g q 48 h for 2 doses in 2nd trimester and repeated in 3rd trimester	34/289 (12)	51/315 (16)	1.4 (0.9–2.1)	31/289 (11)	60/315 (19)	1.8 (1.2–2.7)
Kigozi et al. [66]	Community clusters randomized: treatment or control; subanalysis: TV-positive pregnant women ($N = 277$)	Mtz, 2 g; Cfx, 400 mg; Azm, 1 g po single dose	8/110 (7)	17/94 (18)	2.5 (1.1–5.5)	31/165 (19)	27/112 (24)	1.3 (0.8–2.0)

NOTE. Azm, azithromycin; Cfx, cefixime; Mtz, metronidazole; po, orally; RR, relative risk; t.i.d., three times a day; TV, *Trichomonas vaginalis*.

^a Less than 2500 g.

^b Less than 37 weeks' gestation.

^c Mean gestational age: control group, 39.8 weeks; Mtz-treated group, 39.5 weeks.

and 29 weeks' gestation. Follow-up TV cultures in 529 women demonstrated persistent trichomoniasis in 65% of women in the placebo group and in 7% of women in the treatment group. There was no difference between the groups in the rates of stillbirths, neonatal deaths, or postpartum endometritis.

In 2003, an intent-to-treat subgroup analysis of pregnant women with culture-positive TV in a community cluster antibiotic treatment trial demonstrated that low birth weight was more common in the treatment (azithromycin [1 g], cefixime [400 mg], and metronidazole [2 g]) group (18%) than in the placebo group (7%) (RR, 2.5; 95% CI, 1.1–5.5) [66]. Rates of prematurity were not significantly different between the groups. Unfortunately, there are several limitations to this trial. A lower percentage of infants in the control arm had their weight measured within 1 week of birth. The treatment group had a higher prevalence of HIV infection than the control group (29% vs. 22%; $P = .18$), and there was no follow-up to assess the efficacy of therapy for trichomoniasis and the rate of relapse or reinfection. Because this study used metronidazole, azithromycin, and cefixime, it is also hard to isolate a single drug as a cause of poor pregnancy outcomes. There was no multivariate analysis to take into account possible confounding factors, such as the mother's prepregnancy weight, the presence of other STDs, smoking, or age. Finally, the study was not originally designed for evaluation of treatment for trichomoniasis during pregnancy.

Given the differing methodologies and results of the studies discussed above, more data are needed to define the best management of trichomoniasis in pregnancy. For the time being, patients should be counseled regarding the possible risks (prematurity and low birth weight) and benefits (resolution of vaginitis, prevention of vertical transmission, and interruption of sexual transmission) of treatment. In asymptomatic women, a delay in treatment until after 37 weeks' gestation could be considered, with careful counseling regarding condom use and the risks of sexual transmission. There is no evidence to suggest that asymptomatic pregnant women should be offered routine screening for trichomoniasis.

CONCLUSION

Vaginal trichomoniasis is a common problem that can be associated with serious sequelae. More widespread use of point-of-care diagnostics could aid in the effort to control this often chronic and asymptomatic infection. Although PCR has improved the sensitivity of diagnosis in men and women, it is in limited use. The addition of tinidazole to the treatment armamentarium provides an alternative for treatment of uncomplicated disease and offers greater activity against resistant strains of TV. Although significant clinical resistance to metronidazole is rare, more studies are needed to determine the best medication, dose, and length of therapy for metronidazole-resistant infection.

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