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Nitroimidazole Resistance in *Trichomonas vaginalis* Infection:

A Teachable Moment

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Story From the Front Lines

A previously healthy woman in her 30s presented to an infectious diseases clinic for evaluation of persistent *Trichomonas vaginalis* infection. She had developed vaginal discharge and irritation 2 years earlier after sexual intercourse with a male partner. She was diagnosed with trichomoniasis and treated with oral metronidazole, 2 g, in a single dose. However, her symptoms did not resolve. Over the course of the next 8 months she returned at least 6 times and saw different health care providers for treatment of persistent discharge. Each time, samples were sent for microscopy or nucleic acid amplification testing (NAAT), test results were positive for *T vaginalis*, and she was treated with different nitroimidazole regimens. In sequence, these treatments included oral metronidazole, 500mg, twice daily for 7 days; oral tinidazole, 2 g, once daily for 5 days; oral metronidazole, 500 mg, twice daily plus intravaginal metronidazole for 7 days; oral tinidazole, 2 g, once; oral tinidazole, 2 g, once daily for 5 days; and oral metronidazole, 2 g, daily for 5 days.

None of these regimens led to resolution of the patient's symptoms. When seen in the infectious diseases clinic, she had had persistent vaginal discharge for 2 years. She had not sought additional treatment for more than a year because she had been under the impression that there were no further options available. Importantly, she had not been sexually active since she was first diagnosed with trichomoniasis, and she had completed the full course of each prescribed regimen.

In the infectious diseases clinic, microscopy and NAAT tests showed positive results for *T vaginalis*, and a vaginal sample was sent to the Centers for Disease Control and Prevention (CDC) for resistance testing. Based on in vitro susceptibility testing, the isolate showed a high level of resistance to metronidazole and tinidazole (aerobic minimum lethal concentration, >400 µg/mL; fully susceptible range, <50 µg/mL). Owing to insurance issues, the patient was unable to receive oral tinidazole and intravaginal paromomycin as recommended by the CDC, but she was eventually successfully treated with a regimen of high-dose oral tinidazole, 1 g, 3 times daily for 14 days, and intravaginal boric acid, 600 mg, twice daily for 28 days, a regimen that was developed in consultation with local sexually

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transmitted infection (STI) experts. One month after treatment, the patient's vaginal discharge had resolved, and microscopy and NAAT test results were negative for infection.

Teachable Moment

Trichomoniasis is the most prevalent nonviral STI in the United States and affects an estimated 3.7 million people, which is more than gonorrhea, chlamydia, and syphilis.^{1,2} Women infected with *T vaginalis* are often asymptomatic, but vaginitis, cervicitis, urethritis, and, in women with HIV, pelvic inflammatory disease may develop.³ The most common complaint among women is vaginal discharge, followed by pruritus and dysuria.²

The CDC recommends that patients should be treated initially with 2 g of either metronidazole or tinidazole in a single dose (HIV-positive women should receive oral metronidazole, 500 mg, twice daily for 7 days).

³Cure rates with the oral nitroimidazole regimens are reportedly high, but persistent trichomoniasis has been reported in 12% of HIV-negative and 15% of HIV-positive patients after treatment.² Noncompliance and reinfection, often due to inadequate partner treatment, likely play a role in many cases of persistent infection. However, an estimated 5% of *T vaginalis* isolates may show some degree of resistance to nitroimidazoles.² Unfortunately, *T vaginalis* antimicrobial susceptibility testing (AST) is not routinely available in most laboratories. Samples can be sent to the CDC for AST.³

If reinfection is excluded in patients with persistent trichomoniasis, the CDC recommends treating with oral metronidazole, 500 mg, twice daily for 7 days, and if this regimen fails, 2 g of metronidazole or tinidazole for 7 days. If infection still persists, it is recommended that the sample be sent to the CDC for AST.³ The Figure shows a suggested treatment flow adapted from CDC guidelines.^{3,4} Although treatment failure may be complex and related not only to nitroimidazole resistance, but also to interactions with the resident vaginal microbiota, insufficient drug absorption, or inadequate drug transport to the site of infection, clinical and microbiological cure rates are higher when susceptibility testing results are applied to develop treatment recommendations.^{2,5}

The case described herein illustrates a key lesson: repeated treatment with the same or similar antibiotic regimen without clinical and microbiological response may represent antimicrobial resistance. Although this patient did receive appropriate initial treatment, a failure to recognize the possibility of nitroimidazole resistance after multiple (including high dose) oral regimens led to exposure to unnecessary and ineffective antibiotics, potential for ongoing infection transmission to others, and substantial patient morbidity and distress. Although options for treatment of nitroimidazole-resistant trichomoniasis are limited, alternative regimens, including some involving high-dose nitroimidazoles, intravaginal boric acid, and paromomycin, have been efficacious in refractory cases.^{2,5}

Treatment of trichomoniasis is a priority because of patient morbidity, potential for transmission, and an association with increased risk of HIV acquisition.³ All patients with persistent *T vaginalis* infection should be questioned regarding compliance and partner

treatment. In those without evidence for noncompliance or reinfection whose infection is not cured after high-dose nitroimidazole therapy, additional AST should be sought.

Conflict of Interest Disclosures:

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Figure 1.
Suggested Treatment Flow for Trichomoniasis Management