Clinical knots

Recalcitrant vaginal trichomoniasis

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As *Trichomonas vaginalis* infects the urethra, Bartholin's and Skene's glands, as well as the vagina systemic treatment for trichomoniasis is recommended. The only group of drugs with safe, proved, systemic efficacy is the imidazoles and the most widely used agent is metronidazole. When antimicrobial resistance arises it is likely to be shared across the group.¹ Metronidazole resistant strains have only been reported in patients who have already received treatment with this drug. It is therefore most important that at presentation women are given a regimen which maximises the likelihood of achieving therapeutic levels supported by thorough partner notification to limit the need to provide further treatment.

The failure of women with vaginal trichomoniasis to respond to metronidazole is not uncommon and in most cases probably results from a failure to take the medication as advised or reinfection from an untreated, usually asymptomatic, male sexual partner. The disulfiram-like reaction with alcohol is likely to compromise adherence so the 2 g single dose treatment may achieve better results in cases of poor compliance, whereas the 7 day treatment (400 mg or 500 mg twice a day) is better if reinfection is likely to arise before a contact can be treated. Therapeutic levels of the drug may be related to the patient's weight so consideration should be given to higher dosage regimens in the obese patient. In early cases of persistence the possibility of metronidazole inactivation by vaginal aerobic and anaerobic bacteria² should be covered by prescribing a combination of either amoxycillin or erythromycin with high dose metronidazole or by substituting an alternative imidazole such as tinidazole. Although rare the possibility of a low plasma zinc level³ should also be considered as imidazole re-treatment with an oral zinc supplement may be curative.

Metronidazole resistance is the most likely cause of treatment failure thereafter and strains sent for sensitivity testing from such cases are invariably resistant to metronidazole in aerobic culture (personal communication, no longer routinely available through the Public Health Laboratory Service). Unlike other infections metronidazole resistant trichomoniasis has never been reported arising in population clusters and always appears to be preceded by prior imidazole medication, usually on several occasions. The resistance mechanism is unclear but may have an idiosyncratic basis. This means that no single author or centre has sufficient experience to recommend satisfactory evidenced based measures to manage such cases and many case reports of alleged treatment

successes are prejudiced by the possibility of a coincidental spontaneous resolution.

The size of the problem is difficult to establish although in 1989 a British Cooperative Clinical Group study identified 24 contemporary resistant cases from 18 different centres in the United Kingdom (although not all centres participated).⁴ A variety of therapeutic regimens were described. In the same year in the United States the Centers for Disease Control⁵ estimated that 5% of all *T. vaginalis* isolates displayed some level of resistance to metronidazole. The largest recent series (three cases) was reported in 1997 by Lewis *et al.*,⁶ all with different therapeutic outcomes.

As resistance may be relative rather than absolute most clinicians would persist with imidazoles in high dosage which may include oral, topical, and intravenous preparations, often in combination. Some success has been reported by using metronidazole in this way although changing imidazoles is generally favoured. Tinidazole appears to be the preferred option although niridazole has been postulated as being a useful alternative as it is unaffected by oxygen in aerobic assays. However, in clinical practice the results have been disappointing.

The management of persistent cases thereafter tends to be idiosyncratic and lacks consistency. For every report of apparent success, assuming that spontaneous resolution has not occurred, there are documented cases of failure using similar regimens and no one has collected enough cases to draw any meaningful conclusions. There are also no systemic alternatives so the effect of the available topical medications will be limited. Experimental *in vitro* efficacy does not mean that an agent will have any benefit in resistant cases.

Clinicians faced with the problem of intrasigant vaginitis unresponsive to high dose imidazoles have reported some apparent success with treatments used before the introduction of metronidazole. These include paromomycin, which needs to be prepared in a cream for intravaginal administration at a dose of 250 mg daily for 5–14 days, arsenic pessaries (acetasol) 500 mg daily for 10 days, zinc sulphate douches (1%) in combination with metronidazole, and povidone iodine as a douche or in combination with metronidazole as a pessary. The serendipitous resolution of resistant infection after a woman started using condoms with a single 100 mg nonoxynol-9 pessary suggests that this may be a further therapeutic option. In other studies both nonoxynol-9 and povidone iodine have provided symptomatic relief to women with trichomonal vulvovaginitis without eradicating the infection (see fig 1).

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Figure 1 Management of recalcitrant vaginal trichomoniasis.

Topical azoles (clotrimazole, butaconazole, and fenticonazole), marketed for yeast and fungal infections, have been suggested as they have shown some activity in non-resistant trichomoniasis. However, when used in resistant cases the response has been generally poor although they may provide some symptomatic relief.

Mebendazole and furazolidone are antiprotozoal agents used primarily for bowel infections as they are not absorbed by the gastrointestinal tract. In vitro studies have shown efficacy against metronidazole resistant

T. vaginalis.⁷ Furazolidone is available in Germany as a vaginal pessary but information on its value in resistant trichomoniasis is limited. Mebendazole, when prepared as a vaginal preparation, has proved unsuccessful in established metronidazole resistant cases.

Other measures documented include the use of inactivated lactobacilli as a vaccine, with generally a poor response and the withdrawal of oestrogen replacement treatment in a post menopausal woman. Hydrogen peroxide producing lactobacilli have no protective ability against trichomoniasis unlike bacterial vaginosis so local measures aimed at altering the local bacterial flora are unlikely to be successful.

Finally, researchers have examined other agents in animal and in vitro experiments although there do not appear to be any practical developments. These agents include pyrazoles,⁸ geneticin⁹ (an aminoglycoside lethal to swine at minimum therapeutic doses), and hamycin¹⁰ (a polyene with cytotoxic side effects).

The problem of antibiotic resistance, so well recognised in bacterial infection, does not receive the same prominence when dealing with protozoan infections, where basic therapeutic options are much more limited. For people with metronidazole resistant trichomoniasis or who are unable to take this group of drugs there is a clear need for a safe, systemic, non-imidazole based alternative.

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