

Ineffectiveness of Erythromycin for Treatment of *Haemophilus vaginalis*-Associated Vaginitis: Possible Relationship to Acidity of Vaginal Secretions

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Received for publication 27 August 1979

To assess the efficacy of oral erythromycin in the treatment of nonspecific vaginitis (NSV), we conducted a nonrandom, unblinded pilot study among 17 women with symptoms and signs of NSV. At the completion of treatment, 10 of 13 patients had persistent symptoms, 9 of 13 had persistent abnormal discharge, and 11 of 13 had persistently positive cultures for *Haemophilus vaginalis*. Ten patients with persistent or relapsing NSV and four who did not complete erythromycin treatment were retreated with oral metronidazole, and 14 of 14 showed clinical improvement and eradication of *H. vaginalis*. The susceptibility of 27 clinical isolates of *H. vaginalis* to erythromycin was determined at pH 5.5, 6.0, 6.5, and 7.0. The minimal inhibitory concentration of erythromycin for *H. vaginalis* was approximately 10-fold higher at pH 5.5 than at pH 7.0. Erythromycin is not effective for the treatment of *H. vaginalis*-associated NSV; this may be partly attributable to the reduced activity of this drug in acidic vaginal secretions.

Nonspecific vaginitis (NSV) is a common and still incompletely understood condition characterized by increased and malodorous vaginal discharge not associated with *Trichomonas vaginalis* or yeast infections. Early studies suggested an etiological role for *Haemophilus vaginalis* (4). This role has since been disputed by some and supported by others. Pheifer et al. (7) found that 17 of 18 women with characteristic symptoms and signs of NSV, but only one of 18 matched normal women, had positive cultures for *H. vaginalis*. An association of NSV with quantitatively increased growth of anaerobes from vaginal secretions was also noted (7). Eradication of *H. vaginalis* was significantly correlated with resolution of symptoms and signs of NSV. Thus, although the total etiological picture remains unclear, *H. vaginalis* appears to be associated with the condition.

Treatment of NSV remains a problem. Gardner and Dukes (4) reported success with intravaginal sulfonamide creams and oral tetracycline therapy. However, Pheifer found persistent signs and positive *H. vaginalis* cultures after therapy in 6 of 7 patients treated with sulfonamide cream and in 13 of 15 treated with oral doxycycline. This result might be predicted from in vitro susceptibility testing reported by Mickelsen and McCarthy (Abstr. Annu. Meet. Am. Soc. Microbiol. 1977, A83, p. 14), in which only 55% of *H. vaginalis* strains tested were susceptible to 4 μ g of tetracycline hydrochloride per ml

and none was susceptible to 28 μ g of sulfamethoxazole per ml. Although some investigators (5, 8) have reported that ampicillin is effective, Pheifer found negative cultures for *H. vaginalis* in only 9 of 27 NSV patients treated with ampicillin, and most had persistent symptoms and signs. In contrast, metronidazole has been consistently effective. A regimen of 500 mg by mouth twice daily for 7 days eradicated *H. vaginalis* in all 81 patients treated, with resolution of symptoms and signs in 80. However, the safety of metronidazole has been questioned (9), and its efficacy must be weighed against potential toxicity. Effective alternatives for the treatment of NSV are desirable.

Mickelsen and McCarthy found erythromycin and clindamycin to be the most active of 21 antimicrobial agents tested against *H. vaginalis* in vitro (Abstr. Annu. Meet. Am. Soc. Microbiol., A83, p. 14), with 58 strains susceptible to 0.06 μ g or less of erythromycin per ml. The relative safety of erythromycin and its activity against *H. vaginalis* in vitro led to a pilot study of the therapeutic efficacy of this compound in 17 women referred from Seattle clinics with a diagnosis of *H. vaginalis*-associated vaginitis.

MATERIALS AND METHODS

Initial evaluation and patient selection. All patients underwent a standard interview, pelvic examination, wet mount examination of vaginal secretions, cervical culture for *Neisseria gonorrhoeae*, and vagi-

nal culture for *H. vaginalis*. During the vaginal examination, the presence and amount of abnormal discharge were noted. A 2-ml amount of sterile normal saline was then instilled into the vagina. A sterile cotton swab was used to swab secretions from the vaginal walls into the saline pool. This swab was then used to inoculate a chocolate agar plate (7) for isolation of *H. vaginalis* and to prepare saline and 10% KOH wet mounts, which were immediately examined for clue cells, *T. vaginalis*, and *Candida* species. A cervical swab was inoculated onto a Thayer-Martin plate to rule out *N. gonorrhoeae* infection. The pH of the pooled vaginal secretions was determined by using a pH meter with a combination pH electrode (PHM 61, Radiometer, Copenhagen).

All patients included in the study had an abnormal discharge which was consistent with NSV (Mickelsen and McCarthy, Abstr. Annu. Meet. Am. Soc. Microbiol., A 83, p. 14). Wet mounts showed clue cells and no evidence of *T. vaginalis* or *Candida albicans* infection. An amine-like odor, characteristic of NSV (2), was noted upon addition of 10% KOH to the discharges of 15 of the 17 patients.

Microbiological methods. The chocolate and Thayer-Martin plates were incubated in a candle extinction jar at 35°C and checked for growth at 24 and 48 h. *H. vaginalis* was identified according to the method of Pfeifer et al. (7).

Treatment. Patients were treated with 500 mg of erythromycin orally four times daily for 7 days. They were asked to refrain from sexual intercourse during therapy and return for follow-up visits at 7 days, 3 weeks, and 6 weeks. At each follow-up visit, patients were reexamined as during the initial visit. Those discontinuing erythromycin therapy due to side effects or requiring retreatment at the completion of therapy or thereafter because of persistent signs and symptoms were treated with 500 mg of metronidazole twice daily for 7 days.

Antibiotic susceptibility testing. The in vitro susceptibility of 27 isolates of *H. vaginalis* obtained from women with NSV was determined for erythromycin by the standard agar dilution method (10) at pH 5.0, 5.5, 6.0, 6.5, and 7.0. The pH was adjusted with hydrochloric acid and sodium hydroxide after media had been autoclaved and antibiotics had been added. Peptone-starch-dextrose agar (3) was used in place of Mueller-Hinton agar, which does not support growth of *H. vaginalis*. Plates were inoculated with a Steers replicator, incubated in a CO₂ incubator containing approximately 5% CO₂ in air at 35°C, and examined at 48 h for minimal inhibitory concentrations.

RESULTS

Therapy results. Four patients discontinued erythromycin therapy early in the course of treatment due to nausea, cramping, or diarrhea or all of these. Three others experienced mild nausea or diarrhea, or both, but continued therapy.

All 17 patients were initially culture positive for *H. vaginalis* and negative for *N. gonorrhoeae*. As shown in Table 1, of the 13 women who completed therapy, 11 remained culture positive for *H. vaginalis*. Of these 11, 9 had persistent abnormal discharge and 10 had persistent abnormal odor. The pH of vaginal secretions remained greater than 5.0 in seven of ten women retested after therapy. Seven women were retreated with metronidazole at the first followup visit because of persistent abnormal discharge. Of the remaining six patients, two were lost to follow-up, one remained well, and three had signs and symptoms of NSV and positive cultures for *H. vaginalis* within 6 weeks

TABLE 1. Symptoms, signs, and culture results in women examined after erythromycin therapy^a

Patient no.	<i>H. vaginalis</i> culture	Symptoms	Signs of discharge	Final outcome
1	-	Present	Absent	Symptoms, signs, and <i>H. vaginalis</i> present at 3 weeks; metronidazole given
2	+	Absent	Present	No further followup
3	+	Present	Present	Metronidazole given 7 days
4	+	Present	Present	Metronidazole given 7 days
5	+	Absent	Present	Metronidazole given 7 days
6	+	Present	Present	Metronidazole given 7 days
7	+	Present	Present	Metronidazole given 7 days
8	+	Present	Present	Metronidazole given 7 days
9	+	Present	Present	Metronidazole given 7 days
10	+	Present	Present	Symptoms, signs, and <i>H. vaginalis</i> present at 6 weeks; metronidazole given
11	+	Absent	Absent	Symptoms, signs, and <i>H. vaginalis</i> present at 4 weeks; metronidazole given
12	+	Present	Absent	Symptoms, signs absent <i>H. vaginalis</i> absent at 6 weeks
13	-	Absent	Absent	No further followup

^a Patients 1 through 9 and 13 were examined on day 7 of erythromycin therapy; patients 10 and 11 were examined 7 days after completing therapy; and patient 12 was examined 14 days after completing therapy. With one exception, patients abstained from sexual intercourse throughout the treatment and follow-up period. Patient 11 had intercourse once after therapy, using a condom.

after starting therapy and were retreated with metronidazole.

Thus, 14 patients, including 10 with persistent or relapsing NSV and 4 who could not comply with treatment, were retreated with metronidazole. All 14 became culture negative for *H. vaginalis* and free of symptoms and signs of NSV after 7 days of metronidazole therapy. Eight were reexamined 3 to 6 weeks after treatment, and all remained culture negative and free of symptoms and signs of NSV.

Susceptibility testing results. Minimal inhibitory concentrations (MICs) of erythromycin for the 27 strains of *H. vaginalis* are shown in Table 2. Although 26 of 27 strains had MICs of ≤ 0.03 μg of erythromycin per ml at pH 7.0, the MIC of most strains was approximately 10-fold or more higher at pH 5.5. Due to poor growth, MICs could not be determined at pH ≤ 5.0 .

DISCUSSION

The present study shows erythromycin in an oral dose of 500 mg four times a day for 7 days to be ineffective for NSV, despite high in vitro susceptibility of *H. vaginalis* to erythromycin at pH 7.0.

The failure of erythromycin to eradicate *H. vaginalis* in vivo is not fully explained. Erythromycin may achieve low levels in vaginal fluid

or be inactivated in the vaginal fluid by other bacteria. The influence of pH on activity of erythromycin against *H. vaginalis* probably contributes to the failure, since the pH of vaginal fluid in nonspecific vaginitis is usually 5.0 to 5.5 (1, 3).

ACKNOWLEDGMENTS

This study was approved and supported by the Division of Hospitals and Clinics, Bureau of Medical Services, Public Health Service Project grant no. SEA 76-6-72 and NIH grant no. A112192-02, and by a grant from the Upjohn Co.

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TABLE 2. Influence of pH on the MIC of erythromycin for 27 clinical isolates of *H. vaginalis*

MIC	No. of strains at pH:			
	7.0	6.5	6.0	5.5
≤ 0.03	26	20	1	2
0.06	1	6	11	0
0.125		1	14	3
0.25			1	12
0.50				0
1.0				10
2.0				
4.0				