

Treatment of urinary tract infection by *Gardnerella vaginalis*: A comparison of oral metronidazole versus ampicillin

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ABSTRACT. Treatment options for bacterial vaginosis are numerous, however for urinary tract infection (UTI) by *Gardnerella vaginalis* have been not reported. Our purpose was to compare the efficacy and treatment complications of oral metronidazole versus oral ampicillin for treatment of this condition in a prospective randomized, nonblinded study. Fifty-seven women who had symptoms of UTI and a positive culture for *G. vaginalis* were enrolled in the study. Only forty-five subjects were considered valuable: 25 treated with oral metronidazole 500 mg twice daily for 7 days, and 20 with oral ampicillin 2 g for 10 days. Positive culture was defined as the presence of 10^4 or 10^5 UFC/ml of *G. vaginalis* in pure culture in HBT media. The clinical and bacteriological cure rates were 92% and 96% respectively for metronidazole and 90% in both for ampicillin. Chi-squared analysis reveals no statistical significance between two treatments. Adverse events were common in-patients treated with metronidazole whereas relatively few side effects were experienced in-patients treated with ampicillin. Ampicillin is effective, safe and well-tolerated therapy for UTI by *G. vaginalis*. In contrast oral metronidazole is effective but no safe and bad-tolerated therapy for the same condition.

Key words: *Gardnerella vaginalis*, treatment, metronidazole, ampicillin, urinary tract infection.

INTRODUCTION

Gardnerella vaginalis, a facultative anaerobic, nonmotile, pleomorphic Gram-negative to Gram-variable rod, first described by Leopold in 1953,¹⁵ has been implicated as the predominant organism in Bacterial Vaginosis (BV) by numerous investigators.^{6,9,22} Besides being implicated in BV, *G. vaginalis* and other microorganism associated with this condition such as *Prevotella* sp. and *Bacteroides* sp., have been associated with preterm birth, preterm rupture of membranes, chorioamnionitis, amniotic fluid infection, and puerperal infection.^{4,11,17,19}

However, the importance of *G. vaginalis* in the urinary tract has attracted comparatively little attention. Moy et al¹⁸ recovered *G. vaginalis* from the bladder aspiration urine of patients with reflux nephropathy and from subjects with acute symptoms of urinary tract infection (UTI). Other re-

RESUMEN. La literatura reporta diferentes opciones para tratar la vaginosis bacteriana, sin embargo no se han publicado estudios sobre tratamientos contra *Gardnerella vaginalis* aislada de infección de vías urinarias (IVU). Nuestro objetivo fue comparar eficacia y seguridad de la ampicilina vs metronidazol para tratar esta condición. Se incluyeron 57 pacientes con sintomatología de IVU y cultivo positivo para *G. vaginalis*. De éstas, sólo 45 fueron consideradas para el estudio. 25 fueron tratadas con metronidazol vía oral, 500 mg dos veces al día por siete días y 20 con ampicilina vía oral 2 g por 10 días. Se definió como cultivo positivo cuando se aislaron 10^4 a 10^5 UFC/ml de *G. vaginalis* en cultivo puro en el medio HBT. Se obtuvo cura clínica de 92% y cura bacteriológica de 96% para el metronidazol y 90% para ambos con ampicilina. El análisis por chi cuadrada no revela diferencias estadísticas significativas entre los dos tratamientos. Los efectos colaterales fueron más comunes en los pacientes tratadas con metronidazol mientras que relativamente pocos efectos se presentaron en pacientes tratadas con ampicilina. Se concluye que la ampicilina es un tratamiento efectivo, seguro y bien tolerado para IVU por *G. vaginalis*. En contraste el metronidazol es efectivo pero poco seguro y mal tolerado tratamiento contra la misma condición.

Palabras clave: *Gardnerella vaginalis*, tratamiento, metronidazol, ampicilina, infección de vías urinarias.

searchers have associated *G. vaginalis* with hemorrhagic cystitis,¹ chronic pyelonephritis¹⁶ and symptomatic bacteriuria.²⁰ We have recovered *G. vaginalis* from the midstream urine (MSU) from pregnant and nonpregnant women with and without symptoms of UTI.¹⁰

Treatment options for BV are numerous, The Center for Disease Control and Prevention currently recommends: Metronidazole 500 mg orally twice daily for 7 days; Metronidazole 2 g orally twice; Clindamycin 300 mg orally twice daily for 7 days; and 2% clindamycin vaginal cream 5 g once daily for 7 days.⁵ However, treatment options for UTI by *G. vaginalis* have been no reported in the literature except one case treated for 10 days with oral amoxicillin (2 g/day), and the symptoms resolved,²⁰ and four cases more in the same work treated with metronidazole, doxycycline, ciprofloxacin and sulfamethoxazole-trimethoprim. All responded clinically.

Our purpose was to compare the efficacy and treatment complications of metronidazole vs ampicillin for the treatment of urinary tract infection by *G. vaginalis* in a prospective, randomized nonblinded study.

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METHODS

Setting. This study was done in Primary Care Center Dr. José Castro Villagrana, in Tlalpan, México. Women 16 years of age or older who had symptoms of a urinary tract infection (dysuria, urgency, frequency, and other) a positive culture of urine for *G. vaginalis* were enrolled in the study.

Positive culture. Was defined as the presence of 10^4 or 10^5 CFU/ml of *G. vaginalis* in pure Culture in HBT media.²¹

Collection of MSU. The patient was instructed to hold the labia minora apart and swab the periurethral area with sterile saline. After allowing the first 200 ml of urine to drain in a 20 ml sample (midstream urine sample) was collected.

Identification. *G. vaginalis* was identified on the basis of production of diffuse beta-hemolysis on HBT medium. A gram stain showing small Gram negative to Gram variable bacilli, and a negative catalase reaction.

Patients. Exclusion criterion was a history of hypersensitivity to metronidazole or ampicillin, pregnant women, patients treated for UTI or vaginal infection within 14 days of enrollment, patients with a history of regional enteritis, ulcerative colitis or antibiotic-associated colitis were also excluded from the study. Women treated with metronidazole were told to abstain from alcohol ingestion during the treatment phase of the study.

Women were randomly assigned to one of two treatment groups: oral metronidazole 500 mg twice daily for 7 days or oral ampicillin 2 g for 10 days.

Written informed consent, to join the study was obtained from each patient before enrollment. They were asked to return 10 to 14 days after termination of treatment for questioning, reexamination and urine specimen testing.

The proportion of cured subjects was compared between groups by the chi-square test and Fisher's exact test.

RESULTS

Fifty-seven women were enrolled and randomized to receive one of two pharmaceutical agents. Nine subjects failed to return for the test-of-cure visit and three subjects took their medication inappropriately. Forty-five subjects were considered available: 25 treated with oral metronidazole and 20 treated with ampicillin. A summary of the 25 cases treated with metronidazole is provided in Table 1 and the 20 cases treated with ampicillin in Table 2.

The mean age of subjects was 31.9 (standard deviation [SD] = 11.35) years with a range of 16 to 66 years. The treatment groups did not differ significantly with regard to age, presenting UTI symptoms (dysuria, frequency, urgency, abdominal pain, suprapubic discomfort, hematuria, nocturia and other) or study compliance. The more common symptoms associated a UTI by *G. vaginalis* were dys-

suria and frequency 62.2%; lumbar pain 55.3%; suprapubic discomfort 42.2% and abdominal pain and tenesmo 37.7%.

Two women first treated with ampicillin (cases 7 and 12, table 2) with positive culture and symptoms were treated later with metronidazole and the symptoms resolved. One patient first treated with metronidazole with positive culture (case 12, Table 1) and symptoms was treated later with ampicillin and the symptoms resolved too. Patient 10 (Table 1), with dysuria posttreatment and negative culture wasn't treated.

Adverse events during treatment were common in-patients treated with metronidazole (84%, 21 patients), the most common complaints were: nausea 68%; metallic taste 52%, and anorexia and epigastric pain 20%. Whereas relatively few side effects were experienced in-patients treated with ampicillin, only 6 (30%) patients ($p = 0.005$).

None of the patients stopped their medications as a result of these side effects.

DISCUSSION

Different researches have shown the colonization or infection of the bladder and upper urinary tract by *G. vaginalis* principally in women. Josephson et al reported 2.3% in a Hospital population,¹³ Moy et al, 2.7% of the healthy pregnant female's,¹⁸ Andreu et al 5.6% in open population.³ However, treatment options for UTI by *G. vaginalis* have been not reported. We compared the efficacy of the principal treatment option in bacterial vaginosis, the metronidazole (500 mg, twice daily for 7 days) versus ampicillin (2 g for 10 days). The use of ampicillin for the treatment of BV has often been associated with failure to eradicate *G. vaginalis*, probably due to inactivation of ampicillin by the beta-lactamases produced by vaginal anaerobes. However, this agent may have a role in treating *Gardnerella*-associated infections at extravaginal sites.

Kharsany et al¹⁴ obtained penicillin and ampicillin MIC 90 of 0.5 µg/ml, designating the organisms as susceptible.

Chi-squares analysis reveals no statistical significance between the two modes of treatment, neither clinical or bacteriological cure range. Information concerning the effectiveness of antimicrobial therapy in treating *G. vaginalis* UTI was not well document. However ours results concord with antimicrobial susceptibilities in vitro test for ampicillin reported by Kharsany,¹⁴ apparently the failure in vivo is probably due to inactivation of antibiotic.

Efficacy of metronidazole therapy is the same for VB: 84% according Ferris,⁷ 87% of Fischbach⁸ and 94% of Andres;² for UTI, 92% in this work, and 90% in vitro.¹⁴

Sign and symptoms varied among patients with *G. vaginalis* UTI. Dysuria and frequency were the most common symptoms occurring in 62.2% of the cases. Jose-

Table 1. Summary of cases treated with metronidazole (n=25).

Patient	Age	Symptom first visit	Control culture	Symptoms control	Side effects
1	30	Incontinence; lumbar pain; edema suprapubic discomfort; nocturia	Negative	None	Vomiting
2	57	Dysuria; incontinence; nocturia.	Negative	None	None
3	30	Dysuria; frequency; hematuria; urgency nocturia; tenesmo; poliaquiuria	Negative	None	Metallic taste; nausea
4	26	Frequency; lumbar pain; abdominal pain suprapubic discomfort;	Negative	None	Metallic taste; nausea
5	66	Frequency; urgency; lumbar pain; nocturia;	Negative	None	None
6	27	Dysuria; lumbar pain	Negative	None	Metallic taste anorexia;
7	27	Dysuria; lumbar pain; abdominal pain; suprapubic discomfort	Negative	nausea; headache	Nausea
8	45	Dysuria; frequency; urgency; nocturia; lumbar pain; abdominal pain; suprapubic discomfort; poliaquiuria	Negative	None	Nausea; epigastric pain
9	47	Dysuria; urgency; incontinence	Negative	None	Metallic taste; nausea;
10	16	Frequency; lumbar pain; dysuria; suprapubic discomfort; tenesmo	Negative	anorexia; headache	Nausea
11	21	Dysuria; abdominal pain; lumbar pain suprapubic discomfort; vomiting; tenesmo	Negative	Dysuria	Nausea; vaginal pain
12	30	Dysuria; lumbar pain	G. vaginalis	Dysuria	Metallic taste
13	23	Dysuria; lumbar pain; frequency; tenesmo; poliaquiuria; suprapubic discomfort	Negative	None	Metallic taste; nausea
14	35	Incontinence; urgency	Negative	None	Metallic taste;
15	26	Dysuria; lumbar pain; abdominal pain	Negative	anorexia; nausea	Metallic taste; nausea
16	21	Frequency; lumbar pain; abdominal pain suprapubic discomfort; tenesmo	Negative	Abdominal pain	Nausea; epigastric pain
17	49	Dysuria; frequency; tenesmo; urgency; incontinence; lumbar pain; abdominal pain; suprapubic discomfort	Negative	None	Metallic taste; epigastric pain
18	40	Dysuria; frequency; urgency; poliaquiuria	Negative	Abdominal pain	None
19	40	Frequency; dysuria; urgency suprapubic discomfort; incontinence	Negative	None	Metallic taste; nausea
20	21	Frequency; lumbar pain; abdominal pain	Negative	None	epigastric pain
21	31	Frequency; dysuria; abdominal pain; urgency	Negative	None	Metallic taste; nausea
22	29	Dysuria; lumbar pain; suprapubic discomfort	Negative	None	epigastric pain; anorexia
23	47	Frequency; dysuria; tenesmo; lumbar pain	Negative	None	None
24	24	Frequency; lumbar pain; abdominal pain	Negative	None	Nausea; vaginal pain
25	49	Frequency; tenesmo; suprapubic discomfort	Negative	None	Metallic taste; nausea; headache
					Nausea; epigastric pain
					Metallic taste; anorexia

phson et al¹³ reported 39.5% for dysuria and 34.9% for frequency like the most common symptoms too.

The classic triad of dysuria, frequency and urgency was rarely found (17.7%), Josephson¹³ reported 2.3%.

Respect side effects, the statistical analysis reveals significance between both treatments, adverse events during treatment with ampicillin were uncommon while a greater

percentage of women using metronidazole reported complaints. Rates of 35 to 47% for dislike of oral metronidazole have been reported.¹²

Ampicillin is effective, safe and well-tolerated therapy for urinary tract infection by *G. vaginalis*; in contrast metronidazole is effective, but no safe and bad-tolerated therapy for urinary tract infection by *G. vaginalis*.

Table 2. Summary of cases treated with ampicillin (n=20).

Patient	Age	Control Symptom first visit	Symptoms culture	control	Side effects
1	38	Frequency; lumbar pain; abdominal pain; suprapubic discomfort; fever	Negative	None	Vaginal pruritis
2	19	Dysuria; frequency; fever suprapubic discomfort	Negative	None	None
3	55	Frequency; tenesmo; poliaquiuria nocturia; lumbar pain	Negative	Nnone	Diarrhea
4	25	Dysuria; tenesmo; urgency; poliaquiuria; incontinence;nocturia; abdominal pain	Negative	Nnone	Nausea
5	41	Dysuria; tenesmo; incontinence; lumbar pain; abdominal pain	Negative	None	None
6	29	Dysuria; poliaquiuria; lumbar pain	Negative	None	Generalized pruritis
7	34	Dysuria; hematuria; tenesmo;edema	G. vaginalis	Dysuria	None
8	30	Urgency; frequency; poliaquiuria	Negative	None	None
9	22	Dysuria;frequency;urgency; poliaquiuria	Negative	None	None
10	30	Tenesmo; abdominal pain;	Negative	None	None
11	38	Frequency; urgency; tenesmo	Negative	None	None
12	29	Frequency;incontinence; lumbar pain; suprapubic discomfort; urgency; nocturia; tenesmo; nocturia; edema	G. vaginalis	Dysuria	None
13	24	Frequency; suprapubic discomfort; abdominal pain	Negative	None	None
14	18	Dysuria; lumbar pain; suprapubic discomfort	Negative	None	None
15	19	Frecuency; dysuria; abdominal pain; fever	Negative	None	Nausea
16	21	Frecuency; dysuria tenesmo; lumbar pain	Negative	None	None
17	50	Frecuency; suprapubic discomfort; poliaquiuria	Negative	None	None
18	32	Frecuency; dysuria; suprapubic discomfort	Negative	None	Generalized pruritis
19	33	Dysuria; lumbar pain; tenesmo	Negative	None	None
20	34	Frecuency; abdominal pain; tenesmo; fever	Negative	None	None

Table 3. Efficacy of treatment for UTI by *G. vaginalis* (N=45).

	Metronidazole n=25		Ampicillin n=20		Significance
Type of evaluation	Cure # (%)	Failure # (%)	Cure # (%)	Failure # (%)	
Clinic	23 (92)	2 (8)	18 (90)	2 (10)	p=0.12/ NS
Bacteriologic	24 (96)	1 (4)	18 (90)	2 (10)	p=0.83/ NS
Side effects	Yes # (%)	No # (%)	Yes # (%)	No # (%)	p=0.005
	21 (84)	4 (16)	6 (30)	14 (70)	

NS: No significance.

ACKNOWLEDGMENTS

This research was supported by Family Medicine Department, School of Medicine. Universidad Nacional Autónoma De México. Special thanks to María Ofelia Pedreguera for manuscript preparation assistance.

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