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A RETROSPECTIVE COHORT STUDY ON THE EFFICACY OF METRONIDAZOLE IN PATIENTS WITH TRICHOMONIASIS AT RIMS GENERAL HOSPITAL, SRIKAKULAM

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ABSTRACT

Background: *Trichomoniasis* is a common sexually transmitted disease (STD) among high risk populations. Trichomoniasis is a sexually transmitted infection (STI) usually associated to vaginitis, urethritis, cervicitis and pelvic inflammatory disease, which can cause infertility. **Objective:** The aim of this retrospective longitudinal study was to determine the efficacy of Metronidazole 2gm stat. in Trichomoniasis in High-Risk female patients attended to RIMS, Srikakulam, Andhrapradesh. **Study Design:** A cohort of 300 people who attended the STI Clinic and Gynaecology OP in this province was retrospectively analyzed from September 2011 up to April 2014. **Material and Methods**: Three hundred women (300 from Obstetrics and Gynecology Outpatient Department and STD OPD) patients attending Government General Hospital, attached to the Rajiv Gandhi Institute of Medical Sciences(RIMS), Srikakulam, Andhra Pradesh, India between September 2011 to April 2014, were enrolled in the present study after taking their due consent, with symptoms of trichomoniasis. Their age, occupation, clinical, obstetrical history, and relevant per speculum findings were recorded on a preplanned proforma. Both vaginal swabs and urine samples were subjected to wet smear examination and culture for detection of parasites. **Result:** With 2 gm Metronidazole as a single dose, we did not get any treatment failures in our study. **Summary:** Infections with the sexually transmitted protozoan *Trichomonas vaginalis* are usually treated with metronidazole, a 5-nitroimidazole drug derived from the antibiotic azomycin. Metronidazole treatment is generally efficient in eliminating *T. vaginalis* infection and has a low risk of serious side effects. **Conclusion:** With 2 gm Metronidazole as a single dose, we did not get any treatment failure in our study.Our patients tolerated the dose very well. So, we recommend Metronidazole 2 gm stat. dose for the patients with Trichomoniasis.

KEYWORDS: Metronidazole, *Trichomonas vaginalis, High risk groups.*

INTRODUCTION

Trichomoniasis is a sexually transmitted disease caused by the parasitic protozoan *Trichomonas vaginalis*. It is the most common nonviral sexually transmitted disease, with an estimated 170 million cases occurring worldwide each year.[1] This estimate may well be low, however, since inapparent infection rates are as high as 50% in women and even higher in men.[2] Trichomoniasis has been implicated in causing adverse pregnancy outcomes[3] and has been associated with an increased risk of human immunodeficiency virus (HIV) transmission.[4] Standard treatment for trichomoniasis is commonly with metronidazole, a 5-nitroimidazole used to treat infections caused by certain parasitic protozoa and anaerobic gram-negative bacilli.

Trichomonas vaginalis is a flagellated protozoan that can assume an ameboid form, usually on contact with other cells. Adherence to the epithelial cells of the urogenital tract is an essential step in pathogenesis. One of the most ancient eukaryotes, *T.vaginalis* possesses no mitochondria, instead producing some of its ATP in hydrogen-producing organelles called hydrogenosomes. Carbohydrate metabolism is fermentative, producing acidic end products. The metabolic pathways of *T.vaginalis* share characteristics with both eukaryotes and anaerobic prokaryotes. The activities of these pathways are critical to both *T.vaginalis* susceptibility to metronidazole and the processes by which the parasite develops resistance. *T.vaginalis* lacks the enzymes to synthesize de novo nucleotides and lipids, making it an obligate parasite reliant on salvage pathways. Coupled with the fact that the fermentative metabolism of the protozoan is not a high-efficiency process, this means that *T.vaginalis* is a fastidious organism, requiring an environment rich in nutrients to survive.[5] *T.vaginalis* infection in males is generally mild or asymptomatic. Asymptomatic carriers can serve as vectors for the disease, making it important to treat male partners of infected women to avoid reinfection.

Trichomoniasis in men usually manifests as urethritis clinically similar to other nongonococcal infections, which generally resolves in 10 days or less. Symptomatic men present with a clear or mucopurulent discharge and dysuria.[6] Complications associated with *T.vaginalis* infection include prostatitis, balanoposthitis, epididymitis and infertility.[7]

Trichomoniasis in women usually occurs during the reproductive years. Infection before menarche or after menopause is generally rare and symptoms are mild and transient.[8] The incubation period ranges from 3 to 28 days. Clinical presentation of trichomoniasis in women can include a wide array of symptoms, from asymptomatic to acute inflammatory disease. Unlike in men, where spontaneous resolution of the disease is common, *T. vaginalis* infection can persist for long periods in the female urogenital tract. Up to one-third of asymptomatic women will develop symptomatic infection within 6 months.[9] Mild trichomoniasis usually presents with pruritus and dyspareunia. Vaginal secretion may be present and is generally scanty and mixed with mucus. Acute infection with *T. vaginalis* is characterized by severe pruritus, vaginitis, and vulvitis accompanied by dysuria and dyspareunia. Colpitis macularis (strawberry cervix) can sometimes be seen with the aid of a colposcope as a "speckling" of hemorrhagic spots on the mucosa. Malodorous (fishy) discharge is frothy, yellow or green, mucopurulent and copious[10], as described in "classic" severe vaginitis.

The severity of symptoms in *T.vaginalis* infection is linked to a number of factors. Trichomoniasis is characterized by a rise in the vaginal pH from approximately 4 to as high as 7[11], brought about by a decrease or elimination of endogenous *Lactobacillus* species. This increase in pH creates a better environment for the growth of the parasite.[12] Additionally, certain factors contributing to pathogenicity, such as cell-detaching factor, are inactivated at a pH of less than 5. Cell-detaching factor activity had also been found to be inhibited by estrogen, although it is unknown whether hormones have any other effect on the parasite.[13] The roles played by pH and hormones in trichomoniasis may explain the sobservation that symptoms of the disease are often worse during menstruation.[14] Menstrual blood creates a rich milieu for *T.vaginalis* reproduction at a higher pH than is normally found in the vagina. Additionally, the blood provides increased amounts of iron, which enhances the ability the of *T.vaginalis* to attach to the vaginal epithelium.[15] *T.vaginalis* adheres primarily to the squamous epithelium of the genital tract.[16] Infection is multifocal but usually does not involve the invasion of the parasite into tissue. In men, the external gentitalia, prostate, and epididymis can be infected. The oxidative nature of the male genital tract is hypothesized to be inhibitory to certain pathogenic factors of the protozoan.[17] Zinc, present in prostatic fluid, is also cytotoxic to the parasite.[18] These factors may explain the usually transient nature of infection. Complications, although rare, can result in genitourinary inflammatory disease and sterility. In infected women, the parasite may be found in the vagina, cervix, and bladder, as well as Bartholin's, Skene's and periurethral glands.[19] The vagina is a reducing environment, which may contribute to the activation of some pathogenic mechanisms of *T.vaginalis*.[17] Complications associated with trichomoniasis in women include various inflammatory conditions, cervical erosion, cervical cancer, and infertility. Premature rupture of the placental membranes, contributing to premature labor, and low-birth-weight babies are known perinatal complications.[20] Increased risk of HIV infection due to trichomoniasis is seen in both sexes.[21]

Physical Examination

Women

Vaginal discharge is found in 42% of infected women. The discharge is classically described as thin and frothy; however, this is only seen in about 10% of patients. The discharge is often yellow and sometimes is thick enough to be confused with that seen in candidiasis. Abnormal vaginal odor was found in 50% of infected women and edema or erythema was found in 22-37%, Vaginal pH is often elevated (>4.5).

Colpitis macularis, or strawberry cervix, describes a diffuse or patchy macular erythematous lesion of the cervix. This is a specific sign for trichomoniasis but is visible in only 1-2% of cases without the aid of colposcopy; with colposcopy, colpitis macularis is detected in up to 45% of cases. Together, colpitis macularis and frothy vaginal discharge have a specificity of 99%; individually, they have positive predictive values of 90% and 62%, respectively.

Lower-abdominal tenderness may be present; however, this is described in fewer than 10% of patients. If this occurs, coexisting salpingitis or an intra-abdominal pathology is possible.

Coexisting *Neisseria gonorrhoeae* infection, candidiasis, and bacterial vaginosis are common and may produce a mixed clinical picture.

Most of the symptoms described above are not specific for trichomoniasis and can occur in other vaginal or cervical infections. In one study, the clinician's ability to accurately diagnose *T.vaginalis* infection on the basis of physical findings alone had a positive predictive value of only 47%. Relying on physical examination findings alone misses the diagnosis of most patients with trichomoniasis. Definitive diagnosis requires appropriate laboratory testing.

Men

Most men with trichomoniasis have no physical findings. Infrequently, infected men have abnormal penile discharge. However, the discharge usually is only scant

and thin. Trichomoniasis in men may be associated with local inflammatory states, including balanitis and balanoposthitis. Physical findings of epididymitis and prostatitis may also occur.

Children

In female newborns, *T.vaginalis* acquired during birth may cause vaginal discharge during the first week of life. Respiratory infection of the newborn is also possible. An infected infant may present with fever.

Prepubertal children with trichomoniasis may present with symptoms similar to those seen in the adolescent and adult patient. *T.vaginalis* infection in prepubertal children is suggestive of sexual abuse.

Metronidazole is the treatment of choice for trichomoniasis. Single-dose therapy with 2 g orally is as effective as prolonged therapy with 400 mg thrice daily for 5 days. Single-dose therapy increases drug adherence.

Patients should not consume alcohol during the course of treatment or during the 24 hours after the completion of the medication.

RESULTS

Table 1.

Tot no of cases	T.vaginalis positive in wet mount examination	
	no of cases	percentage
300	53	17.67

A total number of 300 cases were screened for Trichomonas vaginitis by wet mount examination with normal saline and by culture. In wet mount examination with normal saline, 53 cases were positive for T.vaginalis organisms and the remaining 247 cases negative.

Defaulters

Table: 2.

TOT NO OF CASES	Defaulters	patients remained for assessment
53	15	38

Out of 300 cases, 53 cases got T.vaginalis smear positive but, 15 of them defaulted after the first visit leaving 38 patients for assessment. All 38 patients completed the trial according to the plan of study.

Out of 38 patients who completed the trial, 20 patients were given 2gm stat Metronidazole. The remaining 18 patients were given 400 mg of Metronidazole 3 times a day for 5 days.

Response with Metronidazole:
(a) With 2 gm stat. regime:

Table: 3.

Last seen	No of cases followed	Successful	failure rate(%)	admitted for further infection
0 day	53	-	-	-
4th day	20	20	-	-
7th day	20	20	-	-
14th day	20	20	-	-
21st day	20	20	-	-
28th day	20	20	-	-

All the 20 patients completed the trial according to the plan of study. The response of the patients to treatment was shown in the table. There was no failure in the treatment with Metronidazole 2 gms.
(b) With 400 mg of metronidazole, 3 times a day for 5 days.

Table: 4.

last seen	no of cases followed	successful	failure rate(%)	admitted for further infection
0 day	53	-	-	-
4th day	18	18	-	-
7th day	18	18	-	-
14th day	18	18	-	-
21st day	18	18	-	-
28th day	18	18	-	-

All the 18 patients in this 5 day treatment schedule, completed the trial according to the plan of study, the response was good both in the immediate follow-up period and after 4 weeks. There was no treatment failure in this schedule also as observed in the single dose regimen.

Parasitological and clinical response to treatment
Table: 5

Response	Metronidazole 2gm single dose/400mg tid for 5 days	
	n	percentage
(a) Parasitological:		
cure	38	100
failure	0	0
(b) clinical:		
cure or marked improvement in symptoms and signs	38	100
slight or no improvement	0	0

Results were analysed both parasitologically and clinically. All patients showed a uniformly good parasitological response. Examination on the 4th and 7th post treatment days showed that the flagellates had disappeared from the vaginal secretions.A satisfactory clinical response i.e., complete relief of symptom or marked improvement, was seen in 100% patients treated with metronidazole.

Side effects
Subjective side effects were reported by 3 patients, 2 females and one male.

Vomitings occured in 2 female patients while travelling in the bus. These patients who vomited after treatment had negative tests for Trichomonas vaginalis after the 4 weeks follow up. Vomitings occured in a male patient in the clinic itself. The patient who vomited after treatment had negative test for the organism both before and after treatment.

DISCUSSION
Response with Metronidazole
After treatment with metronidazole, the symptoms and signs improved rapidly in all 38 patients satisfied the criterion of cure and 100% efficacy was observed. With single dose treatment, tolerance was good. But in 5 days treatment 3 patients i.e., 2 females and 1male had vomitings, after taking this drug. In other studies clinical trial reports onmetronidazole indicate that a single oral dose of 2 gm cured trichomoniasis in over 95% ofcases when sexual partners are simultaneously treated.

Statistical analysis, however, showed no significant difference between the results of the two schedules of treatment i.e., 400 mg three times a day for 5 days or 2 gm as a single dose both in the immediate follow up period and upto 4 weeks after treatment. It is our opinion that metronidazole seems to be a highly efficacious drug in Trichomoniasis in a single dose of 2 gm. The practical significance of single dose is obvious since it facilities complete treatment of patients as well as consorts right in the physician's presence and thus removing the necessity of relying on the patient to complete a longer course.

Since the results of treatment with 2 gm of metronidazole was good and the incidence of side effects has no difference from the other trials, metronidazole in our opinion, fills the need for an effective well tolerated single dose anti- trichomonal drug.

Infections with the sexually transmitted protozoan *Trichomonas vaginalis* are usually treated with metronidazole, a 5-nitroimidazole drug derived from the antibiotic azomycin. Metronidazole treatment is generally efficient in eliminating *T.vaginalis* infection and has a low risk of serious side effects.

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T. vaginalis infection in males is generally mild or asymptomatic. Asymptomatic carriers can serve as vectors for the disease, making it important to treat male partners of infected women to avoid reinfection. Trichomoniasis in men usually manifests as urethritis clinically similar to other non gonococcal infections, which generally resolves in 10 days or less. Symptomatic men present with a clear or mucopurulent discharge and dysuria.[23] Complications associated with *T. vaginalis* infection include prostatitis, balanoposthitis, epididymitis and infertility.[24]

Trichomoniasis in women usually occurs during the reproductive years. Infection before menarche or after menopause is generally rare, and symptoms are mild and transient.[25] The incubation period ranges from 3 to 28 days. Clinical presentation of trichomoniasis in women can include a wide array of symptoms, from asymptomatic to acute inflammatory disease. Unlike in men, where spontaneous resolution of the disease is common, *T.vaginalis* infection can persist for long periods in the female urogenital tract. Up to one-third of asymptomatic women will develop symptomatic infection within 6 months.[26]

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CONCLUSIONS

T. vaginalis infection has in the past been considered a "nuisance" disease of women and a problem of developing countries. However, increasing global infection rates, pregnancy complications, and increased susceptibility to HIV and other sexually transmitted diseases make it clear that safe, effective, and affordable treatment of trichomoniasis is essential.

Humans are the only known host of *T vaginalis*. Transmission occurs predominantly via sexual intercourse. The organism is most commonly isolated from vaginal secretions in women and urethral secretions in men. It has not been isolated from oral sites and rectal prevalence appears to be low in men who have sex with men.[38]

Women with trichomoniasis may be asymptomatic or may experience various symptoms, including a frothy yellow-green vaginal discharge and vulvar irritation. Men with trichomoniasis may experience nongonococcal urethritis but are frequently asymptomatic.[39]

Trichomoniasis is thought to be widely underdiagnosed due to a variety of factors, including a lack of routine testing,[40] the low sensitivity of a commonly used diagnostic technique (wet mount microscopy),[41] and nonspecific symptomatology. Self-diagnosis and self-treatment or diagnosis by practitioners without adequate laboratory testing may also contribute to misdiagnosis.

Testing is recommended for *T vaginalis* in all women seeking care for vaginal discharge and screening for *T vaginalis* in women at high risk of STI.[42]

Sex partners of infected women should also be treated. Both patient and partner should abstain from sex until pharmacological treatment has been completed and they have no symptoms. Infected women who are sexually active have a high rate of reinfection; thus, rescreening at 3 months post treatment should be considered.[42] Currently, no data are available on rescreening men.

Oral metronidazole is the treatment of choice and may be administered as either a single 2-g dose or as prolonged therapy with 400 mg thrice daily for 5 days. Tinidazole (single 2-g dose) is an FDA-approved alternative to metronidazole that has been shown to be equally effective in clinical trials.[43] Topical treatments are not recommended due to inadequate therapeutic levels.

Treatment with oral metronidazole has not been shown to have teratogenic effects[44] and may prevent transmission to the infant. The CDC currently recommends that infected symptomatic pregnant females be treated with 2 g metronidazole in a single dose. Infected asymptomatic pregnant women may wish to defer treatment to after 37 weeks' gestation.[42]

Drug resistance is rare, despite the prevalent use of nitroimidazole drugs in the treatment of trichomoniasis. Treatment failures may require a higher-dose metronidazole regimen or the use of a different nitroimidazole (eg, tinidazole).

REFERENCES

1. Gerbase, A. C., J. T. Rowley, D. H. Heymann, S. B. F Berkeley and P. Piot. 1998. Global prevalence and incidence estimates of selected curable STDs. Sex. Transm. Dis., 74(Suppl. 1): S12-S16. [PubMed].
2. Fouts, A. C. and S. J. Kraus. 1980. *Trichomonas vaginalis*: a re-evaluation of its clinical presentation and laboratory diagnosis. J. Infect. Dis., 141: 137-143. [PubMed].
3. Heine, P. and J. A. MacGregor. 1993. *Trichomonas vaginalis*: a re-emerging pathogen. Clin. Obstet. Gynecol., 36: 137-144. [PubMed].
4. Cameron, D. E. and N. S. Padian. 1990. Sexual transmission of HIV and the epidemiology of other sexually transmitted diseases. AIDS, 4(Suppl. 1): S99-S103. [PubMed].
5. Petrin, D., K. Delgaty, R. Bhatt, and G. E. Garber. 1998. Clinical and microbiological aspects of *Trichomonas vaginalis*. Clin. Microbiol. Rev., 11: 300-317. [PMC free article] [PubMed].
6. Krieger, J. N. 1990. Epidemiology and clinical manifestations of urogenital trichomoniasis in men, 235-245. *In* B. M. Honigberg (ed.), Trichomonads parasitic in humans. Springer-Verlag, New York, N.Y.
7. Krieger, J. N. 1984. Prostatitis syndromes: pathophysiology, differential diagnosis, and treatment. Sex. Transm. Dis., 11: 100-112. [PubMed].
8. Rein, M. F. 1990. Clinical manifestations of urogenital trichomoniasis in women, 225-234. *In* B. M. Honigberg (ed.), Trichomonads parasitic in humans. Springer-Verlag, New York, N.Y.
9. Heine, P. and J. A. MacGregor. 1993. *Trichomonas vaginalis*: a re-emerging pathogen. Clin. Obstet. Gynecol., 36: 137-144. [PubMed].
10. Wolner-Hanssen, P., J. N. Krieger, C. E. Stevens, N. B. Kiviat, L. Koutsky, Critchlow, T. DeRouen, S. Hillier, and K. K. Holmes. 1989. Clinical manifestations of vaginal trichomoniasis. JAMA, 261: 571-576. [PubMed].
11. Anorlu, R. I., A. F. Fagbenro-Beyioku, T. Fagorala, O. O. Abudu, and H. S. Galadanci. 2001. Prevalence of *Trichomonas vaginalis* in patients with vaginal discharge in Lagos, Nigeria. Niger. Postgrad. Med. J., 8: 183-186. [PubMed].
12. Goode, M. A., K. Grauer and J. G. Gums. 1994. Infectious vaginitis. Selecting therapy and preventing recurrence. Postgrad. Med., 96: 85-98. [PubMed].
13. Garber, G. E., L. T. Lemchuk-Favel, and G. Rousseau. 1991. Effect of β-estradiol on production of the cell detaching factor of *Trichomonas vaginalis*. J. Clin. Microbiol., 29: 1847-1849. [PMC free article] [PubMed].
14. Rein, M. F., and T. A. Chapel. 1975. Trichomoniasis, candidiasis, and the minor venereal diseases. Clin. Obstet. Gynecol., 18: 73-88. [PubMed].
15. Lehker, M. W., R. Arroyo and J. F. Aldrete. 1991. The regulation by iron of the synthesis of adhesins and cytoadherence levels in the protozoan

parasite *Trichomonas vaginalis*. J. Exp. Med., 171: 2165-2170. [PMC free article] [PubMed].
16. Gupta, P. K. and J. K. Frost. 1990. Cytopathology and histopathology of the female genital tract in*Trichomonas vaginalis* infection, 274-290. *In* B. M. Honigberg (ed.) Trichomonads parasitic in humans. Springer-Verlag, New York, N.Y.
17. Alderete, J. F., and D. Provenzano. 1997. The vagina has reducing environment sufficient for activation of *Trichomonas vaginalis* cysteine proteinases. Genitourin. Med., 73: 291-296. [PMC free article] [PubMed].
18. Krieger, J. N. and M. F. Rein. 1982. Zinc sensitivities of *Trichomonas vaginalis*: in vitro studies and clinical implications. J. Infect. Dis., 146: 341-345. [PubMed].
19. Alderete, J. F., and D. Provenzano. 1997. The vagina has reducing environment sufficient for activation of *Trichomonas vaginalis* cysteine proteinases. Genitourin. Med., 73: 291-296. [PMC free article] [PubMed].
20. Wolner-Hanssen, P., J. N. Krieger, C. E. Stevens, N. B. Kiviat, L. Koutsky, Critchlow, T. De Rouen, S. Hillier, and K. K. Holmes. 1989. Clinical manifestations of vaginal trichomoniasis. JAMA, 261: 571-576. [PubMed].
21. Sorvillo, F. and P. Kerndt. 1998. *Trichomonas vaginalis* and amplification of HIV-1 transmission. Lancet, 351: 213-214. [PubMed].
22. Petrin, D., K. Delgaty, R. Bhatt, and G. E. Garber. 1998. Clinical and microbiological aspects of*Trichomonas vaginalis*. Clin. Microbiol. Rev., 11: 300-317. [PMC free article] [PubMed].
23. Kuberski, T. 1980. *Trichomonas vaginalis* associated with nongonococcal urethritis and prostatitis. Sex. Transm. Dis., 7: 134-136. [PubMed].
24. Mardh, P. A. and S. Colleen. 1975. Search for urogenital tract infections in patients with symptoms of prostatitis. Studies on aerobic and strictly anaerobic bacteria, mycoplasmas, fungi, trichomonads and viruses. Scand. J. Urol. Nephrol., 9: 8-16 [PubMed].
25. Rein, M. F. 1990. Clinical manifestations of urogenital trichomoniasis in women, 225-234. *In* B. M. Honigberg (ed.), Trichomonads parasitic in humans. Springer-Verlag, New York, N.Y.
26. Heine, P. and J. A. MacGregor. 1993. *Trichomonas vaginalis*: a re-emerging pathogen. Clin. Obstet. Gynecol., 36: 137-144. [PubMed].
27. Knox, R. J., R. C. Knight, and D. I. Edwards. 1981. Misonidazole-induced thymidine release from DNA. Biochem. Pharmacol., 30: 1925-1929. [PubMed].
28. Anorlu, R. I., A. F. Fagbenro-Beyioku, T. Fagorala, O. O. Abudu, and H. S. Galadanci. 2001. Prevalence of *Trichomonas vaginalis* in patients with vaginal discharge in Lagos, Nigeria. Niger. Postgrad. Med. J., 8: 183-186. [PubMed].
29. Goode, M. A., K. Grauer and J. G. Gums. 1994. Infectious vaginitis. Selecting therapy and preventing recurrence. Postgrad. Med., 96: 85-98. [PubMed].
30. Garber, G. E., L. T. Lemchuk-Favel and G. Rousseau. 1991. Effect of β-estradiol on production of the cell detaching factor of *Trichomonas vaginalis*. J. Clin. Microbiol., 29: 1847-1849. [PMC free article] [PubMed].
31. Rein, M. F. and T. A. Chapel. 1975. Trichomoniasis, candidiasis and the minor venereal diseases. Clin. Obstet. Gynecol., 18: 73-88. [PubMed].
32. Lehker, M. W., R. Arroyo, and J. F. Aldrete. 1991. The regulation by iron of the synthesis of adhesins and cytoadherence levels in the protozoan parasite *Trichomonas vaginalis*. J. Exp. Med., 171: 2165-2170. [PMC free article] [PubMed].
33. Gupta, P. K. and J. K. Frost. 1990. Cytopathology and histopathology of the female genital tract in *Trichomonas vaginalis* infection, 274-290. *In* B. M. Honigberg (ed.) Trichomonads parasitic in humans. Springer-Verlag, New York, N.Y.
34. Alderete, J. F. and D. Provenzano. 1997. The vagina has reducing environment sufficient for activation of *Trichomonas vaginalis* cysteine proteinases. Genitourin. Med., 73: 291-296. [PMC free article] [PubMed].
35. Krieger, J. N. and M. F. Rein. 1982. Zinc sensitivities of *Trichomonas vaginalis*: in vitro studies and clinical implications. J. Infect. Dis., 146: 341-345. [PubMed].
36. Lossick, J. G. 1990. Treatment of sexually transmitted diseases. Rev. Infect. Dis., 12(Suppl.6): S665-S681. [PubMed].
37. Sorvillo, F. and P. Kerndt. 1998. *Trichomonas vaginalis* and amplification of HIV-1 transmission. Lancet, 351: 213-214. [PubMed].
38. Addis, M. A., P. Rappelli, A. M. P. de Andrade, F. M. Rita, M. M. Colombo, P. Cappuccinelli and P. L. Fiori. 1999. Identification of *Trichomonas vaginalis* α-actinin as the most common immunogen recognized by the sera of women exposed to the parasite. J. Infect. Dis., 180: 1727-1730. [PubMed].
39. Alderete, J. F. 1984. Enzyme linked immunosorbent assay for detecting antibody to *Trichomonas vaginalis*: use of whole cells and aqueous extract as antigen. Br. J. Vener. Dis., 60: 164-170. [PMC free article] [PubMed].
40. Aburel, E., G. Zervos, V. Titea, and S. Pana. 1963. Immunological and therapeutic investigations in vaginal trichomoniasis. Rom. Med. Rev., 7: 13-19. [PubMed].
41. Alcalde, E., L. Perez-Garcia, I. Dinares, G. H. Coombs and J. Frigola. 1992. Synthesis and antitrichomonal activity of azinium (azolium) 4-nitrobenzimidazolate betaines and their derivatives. Eur. J. Med. Chem., 27: 171-176.
42. Abraham, M. C., M. Desjardins, L. G. Filion and G. E. Garber. 1996. Inducible immunity to*Trichomonas vaginalis* in a mouse model of vaginal infection. Infect. Immun., 64: 3571-3575. [PMC free article][PubMed].

43. Muller, M. 1986. Reductive activation of nitroimidazoles in anaerobic microorganisms. Biochem. Pharmacol., 35: 37-41. [PubMed].