

Vaginal Infection: Review Article

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Abstract—Vaginitis is a disorder characterized regarding to abnormal bad odor vaginal discharge, discomfort , itching, and burning. Bacterial vaginosis, particularly *Gardnerella vaginalis*, vulvovaginal candidiasis, particularly *Candida albicans*, and trichomoniasis are the most common causes of vaginitis. When a cause is established, bacterial vaginosis is implicated in 40% to 50% of cases, with vulvovaginal candidiasis accounting for 20% to 25% of cases and trichomoniasis accounting for 15% to 20% of cases. Physical examination , symptoms, , and laboratory testing are used for final identification. *Gardnerella vaginalis* DNA or vaginal fluid sialidase activity, as well as Gram stain, are now available in newer laboratory assays. A mixture of clinical manifestations, as well as potassium hydroxide microscopy, are used to diagnose vulvovaginal candidiasis. Culture and DNA probe testing are also available. For such diagnosis of trichomoniasis in asymptomatic or high-risk women, molecular approaches (nucleic acid amplification) are indicated. This study aimed to review the most recent knowledge on vaginal infection, with the most common causal agents being bacteria, yeast, and parasites **Keywords**—component, formatting, style, styling, insert

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I. INTRODUCTION

A. Vaginal infection

Inflammation of the vaginal canal is also known as vaginitis. It's caused by an imbalance of yeast and bacteria in the vaginal microflora. Vaginal yeast infections, bacterial vaginosis, and other sexually transmitted illnesses can all produce variations in vaginal discharge (1).

Vaginitis is well-defined as an infection caused by a microorganisms, also an unusual sign of a bacteria, parasite, or fungal that occurs in small amounts. Gardnerella, Neisseria gonorrhoeae, Trichomonas vaginalis, and Candida albicans infections are the most common (2-4).

A diverse diversity of anaerobic and aerobic microorganisms makes up the vaginal flora of healthy women. The species Lactobacillus (Döderlein Bacillus) is the most common (5). Because of vaginal disorders, lactobacilli serve a vital role in maintaining the natural flora of the vagina, especially during pregnancy (6). Lactobacillus species boost the body's defenses against infections and keep opportunistic microorganisms at bay. Estrogen promotes the

maturation, proliferation, and storage of glycogen in vaginal epithelial cells at higher levels (VEC). Lactobacilli thrive in an acidic environment provided by glycogen metabolism (7).

B. Sign and symptoms of vaginitis

Discharge with a change in color and a foul odor, burning, itching, pain in the pelvic or during sexual intercourse are the most common symptoms (8). Infections, vaginal flora imbalances, and pH abnormalities are all possible causes of abnormal discharge. Occasionally, there is no established cause for atypical vaginal discharge. In one study, about 34 percent of women who came to the clinic with vaginal discharge or a foul odor in their vagina had bacterial vaginosis, whereas 23 percent had vaginal candidiasis (9). A potassium hydroxide (KOH) test or a vaginal pH study may be done to help in the diagnosis of abnormal vaginal discharge. Vaginitis is a condition in which abnormal discharge is gone with burning, irritation, or itching on the vulva. Bacteria, Candida spp., and Trichomonas sp. are the most relevant reasons for vaginitis (10,11). Each causative agent of vaginitis has signs and symptoms (12), as illustrated in table (1).

TABLE I. SIGN AND SYMPTOMS OF VAGINITIS

TABLE 1				
Signs and Symptoms of Vaginitis				
Diagnosis	Etiology	Symptoms	Signs	Other risks
Bacterial vaginosis	Anaerobic bacteria (Prevotella, Mobiluncus, Gardnerella vaginalis, Ureaplasma, Mycoplasma)	Fishy odor; thin, homogeneous discharge that may worsen after intercourse; pelvic discomfort may be present	No inflammation	Increased risk of HIV, gonorrhea, chlamydia, and herpes infections
Vulvovaginal candidiasis	Candida albicans, can have other Candida species	White, thick, cheesy, or curdy discharge; vulvar itching or burning; no odor	Vulvar erythema and edema	—
Trichomoniasis	Trichomonas vaginalis	Green or yellow, frothy discharge; foul odor; vaginal pain or soreness	Inflammation; strawberry cervix	Increased risk of HIV infection Increased risk of preterm labor Should be screened for other sexually transmitted infections
Atrophic vaginitis	Estrogen deficiency	Thin, clear discharge; vaginal dryness; dyspareunia; itching	Inflammation; thin, friable vaginal mucosa	—
Irritant/allergic vaginitis	Contact irritation or allergic reaction	Burning, soreness	Vulvar erythema	—
Inflammatory vaginitis	Possibly autoimmune	Purulent vaginal discharge, burning, dyspareunia	Vaginal atrophy and inflammation	Associated with low estrogen levels

HIV = human immunodeficiency virus.
Information from references 10, 14, and 15.

1-Bacterial vaginitis (BV)

Bacteria such as Staphylococcus aureus, Escherichia coli, Group B Streptococci (GBS), Listeria, Mycoplasma, and Ureaplasma species can cause aerobic vaginitis (13).

Gardnerella vaginalis, *Prevotella*, *Bacteroides*, and *Mobiluncus* species can also cause bacterial vaginosis (14). Other organisms associated with Bacterial vaginitis (BV) include *Atopobium vaginae*, *Megasphaera* spp, *Eggerthella* spp, and *Leptotrichia* spp (15). Bacterial vaginosis occurs in 40 percent to 50 percent of vaginal infection cases (16).

The vagina suffers from a decrease in lactobacilli and an increase in a variety of anaerobic bacteria, the most prevalent of which is *Gardnerella vaginalis* (17). A gram stain demonstrating of lactobacilli and a polymicrobial gram negative variable rods, and cocci is the gold standard for diagnosis. Oral or intravaginal antibiotics, as well as lactobacillus, can be used to treat BV (18). According to Swidsinski et al. (2014), BV- could be borne by polymicrobial biofilm "clue cells" which are epithelial cells of vagina covered with coccobacillary bacteria (19). Virulent factors of *Gardnerella* spp. like cytotoxicity, adhesion, and biofilm formation are not like other types of BV bacteria .

To make the diagnosis, thin, homogeneous discharge, a positive whiff test, the presence of clue cells on microscopy, Gram stain, and vaginal pH greater than 4.5 are all necessary. When compared to Gram stain and molecular test with *Gardnerella vaginalis* DNA probes or detection of vaginal fluid sialidase activity showed higher sensitivity ranged 92-100% and specificity ranged 92- 98 % (20,21).

C. Pathogenesis

A biofilm generated by *Gardnerella vaginalis* and other species like *Mobiluncus mulieris*, *A. vaginae*, and *Prevotella bivia* are related to bacterial vaginosis (22,23). A polymicrobial biofilm cause the high recurrence rate of BV, as it protects bacteria from lactic acid, H₂O₂, bacteriocins, and antibiotics that used as treatment (such as flagyl and tinidazole), as well as provides resistance against immunity, for example preventing macrophage phagocytosis or chemotaxis (24-26,22). Gene expression of antimicrobial resistance proteins by *G. vaginalis* consider special relevance. Figures 1 A&B depicted clue cells under a microscope, while Figure 1C depicted vaginal and cervix discharge (22).

Despite the fact that *Lactobacillus iners* and *Lactobacillus crispatus* have the same inhibitory effects on BV-associated bacteria adherence (27), *G. vaginalis* adherence was increased in the presence of *Lactobacillus iners*, which could be because of *L. iners*'s limited protective activity.

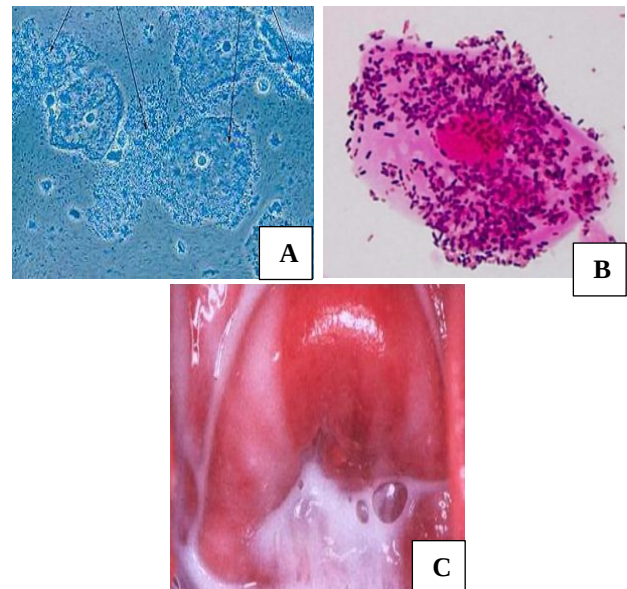


Fig. 1. A, B: vaginal epithelial cell infected with Gv- and Gv+ bacterial species including *G. vaginalis*, revealing of Clue cells. C: Abnormal vaginal & cervix discharge

D. Diagnosis

1-Despite numerous molecular and genomic investigations undertaken at the species or micro biome level, no consensus has been reached on the group of bacteria which may cause actual BV (28,29). High numbers of *L. iners* in BV could be due to its genetic makeup altering vaginal habitats (30). For example, BV demonstrated the expression of genes involved in glycogen, mannose, and maltose breakdown (31).

2-Clinically , BV is identified by the Nugent score (32). Microscopic examination and vaginal swab culture are used to detect changes in the vaginal environment (33).

3-Quantification of Gram-stained bacteria, distinct vaginal morphotypes, and the detection of clue cells are used to diagnose BV (34).

4-Finally, Amsel's criteria for a positive BV diagnosis involves saline microscopy and have been improved via the existence of a thin watery homogenous discharge, high vaginal pH (>4.5), around 20 percent of clue cells , and a fishy amine odor after adding 10% of KOH to vaginal discharges (whiff test) (35).

E. Treatment

BV has Increased antibiotic resistance and different sensitivity patterns in vitro to flagyl and secnidazole (36).

2-Candida vaginitis

Vulvovaginal candidiasis (VVC) is caused by an excess of yeasts, primarily *Candida albicans* that are part of the vaginal flora (37). One of the most prevalent causes of infectious vaginitis is a vaginal yeast infection, which can be caused by both *C. albicans* and non-*albicans* yeast (38,39). Further *Candida* species for example *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *Saccharomyces cerevisiae* account for 1-2 percent of the total (40). Seventy percent of women will contract candida at some point in their lives (41). In yeast infections, vaginal discharge is often white, thick, odorless, and clumpy (Cottage cheese-like) (42,43), accompanying vaginal itching, irritation, burning, soreness,

and pain during urination or intercourse (41). Taking antibiotics, diabetes, pregnancy, and HIV/AIDS are all risk factors, although kind of underwear, tight clothing, and personal cleanliness are not (44, 45).

F. Pathogenesis

During *Candida* vulvovaginitis, *Candida* species penetrate the vagina's mucosal lining. This causes *Candida* species to be drawn to the vagina's mucosal surface as an inflammatory response (46).

Many factors cause *Candida* spp. infection are include : multiple transcriptional trails, morphological and phenotypic switching, biofilm formation, evasion of phagocytosis, adhesion and invasions, extracellular hydrolytic enzymes, metabolic flexibility, genome plasticity, and the ability to adapt to changes in the environment. The fact that there are many connections, and relations between altogether of these factors, are unique features that show significant roles in the development of *Candida* infections (47).

G. Diagnosis

Vaginal candidosis can be diagnosed by looking at a person's medical history, looking at their symptoms, and looking at the yeast in their blood or urine. (48)

1- A wet amount of yeast (hyphae) can be seen with a microscope, and it can also be grown in a lab. Antigen tests can also be done to see if the yeast is preset (49-50).

2- Sabouraud glucose agar is the most common medium for cultures. Chrome agar, on the other hand, is thought to be sensitive and reliable (49).

3-A woman with typical symptoms had positive yeast hyphae on a 10% KOH preparation (49) in the third step.

4-Antigen or DNA probe testing (51-53).

H. Treatment

Antifungal drugs that can be used inside the vaginal canal or a single dose of fluconazole taken orally are commonly used to treat vaginal candidiasis. For serious infections that do not improve, more treatments may be required. These therapies include taking higher doses of fluconazole or using other vaginal drugs including boric acid, nystatin, or flucytosine (54). Figures 2 A,B exhibit *candida albicans* cultivated on Sabouraud agar with gram staining showing budding and hyphae, while Figure 2C shows vulvovaginal candidiasis with cheesy discharge.

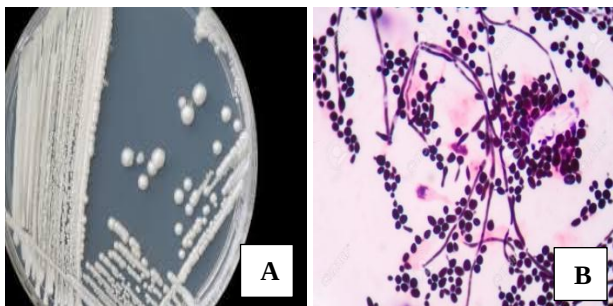


Fig. 2. A: culture of *candida* on Sabouraud glucose agar B: showed budding yeast cells with pseudohyphae. C: cheesy like discharge (Vulvovaginal candidiasis)

I. Trichomonal vaginitis

The most prevalent cause is *Trichomonas vaginalis*. It has been discovered to be linked to sexually transmitted diseases (STD). Trichomoniasis is also found in postmenopausal women, with trichomoniasis cases ranging from 15% to 20% (55). *Trichomonas vaginalis* is regarded as a primordial eukaryote due to it is anaerobic metabolism and lack of mitochondria. It is recently found to have hydrogenosomes (56). *T. vaginalis*, like other *Trichomonas* species, has a great number of transposable elements (TEs) in its huge haploid genome of 160 Mb (57). *Trichomonas vaginalis* has recently been discovered to have meiosis-specific genes, a cyst-like stage with a cell wall, despite the fact that *T. vaginalis* is thought to be asexual and only present as a trophozoite-stage. This could result in a reassessment of the treatment aspect (58,59). *T. vaginalis* is a flagellate protozoan parasite that causes vaginitis, and described clinically by severe signs and symptoms. Trichomoniasis caused 140.8 million cases worldwide in 2015, a 15.4% increase from 2005 to 2015 (60). *T. vaginalis* is a sexually transmitted infection that has a significant recurrence rate, particularly if the male partner is not treated.

In terms of signs and symptoms, women with *T. vaginalis* may have a yellowish-green discharge with a frothy foul odor in nature.

In addition to soreness and vulvar itching accompanied by dysuria and dyspareunia, erythematous or "strawberry patches" in the vaginal and cervix have been reported (61). In rural South Africa, there was a significant prevalence of Vaginal trichomoniasis, which is mostly asymptomatic (62).

J. Pathogenesis

The vaginal flora can be divided into five community state types, with lactobacilli dominating the first four, and anaerobic bacteria (e.g. *Gardnerella vaginalis*) and mollicutes (e.g. *Mycoplasma* spp.) dominating the fifth (63). *T. vaginalis* is linked to CST-IV, which raises vaginal pH, and the presence of particular anaerobic bacteria is linked to *T. vaginalis* acquisition. Lactobacilli thrive in an acidic environment (pH 4.5). (64,65). The interesting fact is that CST-IV improved *T. vaginalis* adherence to epithelial cells by forming a biofilm (66), and both of them can integrate vaginal epithelium by disrupting intercellular connections, although lactobacilli cannot (67). Pinhenio et al. (2018) found that *Lactobacillus gasseri* strain ATCC 9857 inhibits *T. vaginalis* adherence to host cells in a contact-dependent

manner, and that this strain can even displace trichomonads away from vaginal epithelial cells (68). Aggregation-promoting factor 2 (APF-2) is responsible for this remarkable ability, which is encoded by lactobacilli. In addition, *T. vaginalis* have the ability to kill bacteria by expressing 9 peptidoglycan hydrolases of the NlpC/P60 family (69).

T. vaginalis kills epithelial cells in two different ways. Direct cell contact and the release of cytotoxic compounds are two ways that cytotoxic substances can be released. It also attaches to host plasma proteins, blocking the alternative complement pathway and host proteinases from recognizing the parasite. Both, the number of polymorphonuclear leukocytes and the vaginal pH will increase during infection. PMNs are the most common host immune respond against *T. vaginalis*, and they react to trichomonad chemotactic chemicals (70). During infection, Both locally and in serum, an antibody response against *T. vaginalis* infection has been reported (71).

K. Diagnosis

1-Wet preparation: it revealed the presence of infection by showing motile trichomonads in the samples. However, women's sensitivity is 45–60 percent, while men's is even lower (72).

2-Pap smear or cervical smear with normal cervix squamous cells (pink/blue) and *T. vaginalis* appear as tiny blue patches (72).

3-Culture: Trichomonad culture has a greater sensitivity than microscopy, but it can take up to five days to provide a result. The 'gold standard culture' was modified Diamond media, however molecular testing has found to be more sensitive (73).

4- Nucleic Acid Amplification Techniques (NAATs) have highest sensitivity for detecting *T. vaginalis*. This technique identifies *T. vaginalis* DNA in vaginal or endocervical swabs, as well as urine samples from male and female, with high sensitivity and specificity (97% ,99% respectively) (74–77). *T. vaginalis* under a microscope and vaginal discharge illustrated in in Figure 3A, B, 3C.

5- Recently *Trichomonas V*® antigen-based rapid diagnostic strip test was introduced but with no data on its reliability and should not be considered as an alternative test (78).

L. Treatment

As an anti-trichomonadal chemotherapy, metronidazole is still the drug of choice (79). A seven-day regimen of 500 mg twice daily was prescribed. During the course of 5-nitroimidazoles, alternate treatments such as secnidazole or new compounds are recommended (80-82)

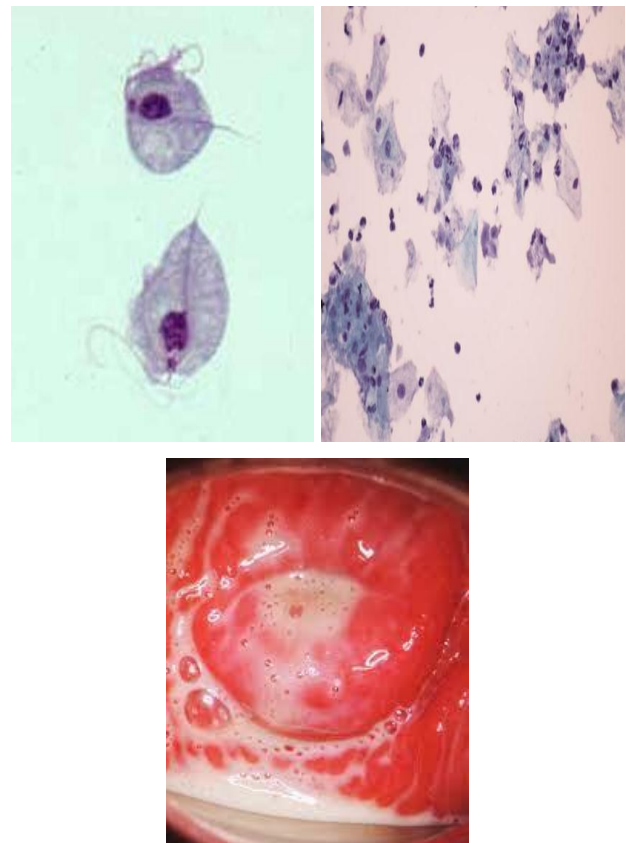


Fig. 3. A: showed *Trichomonas vaginalis* diagnosis under microscope by Giemsa stain. B: showed *Trichomonas vaginalis* diagnosis under microscope by pap smear C: Frothy vaginal discharge with *Trichomonas vaginalis*

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III. REFERENCES

- 1- Rice, Alexandra "Vaginal Discharge". *Obstetrics, Gynaecology & Reproductive Medicine*. (2016) ,26 (11): 317–323
- 2- Coleman JS, Gaydos CA, and Witter F. *Trichomonas vaginalis* Vaginitis in Obstetrics and Gynecology Practice: New Concepts and Controversies. *Obstetrical & Gynecological Survey* .2013; 6868: 43-50.
- 3- Gülmezoglu AM and Azhar M. Interventions for Trichomoniasis in Pregnancy (Review). *Cochrane Database of Systematic Reviews*. 2011; 5:CD000220
- 4- da Silva DS. Bacterial Vaginosis in Portugal: Diagnosis of *Gardnerella vaginalis* and *Atopobium vaginae* in Healthy or Symptomatic Women. *Citeseer*. (2012)
- 5-Lamont RF, Sobel JD, Akins RA, Hassan SS, Chaiworapongsa T, Kusanovic JP, Romero R. The vaginal microbiome: new information about genital tract flora using molecular based techniques. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2011;118(5):533-49.

- 6-Lidbeck A, Nord CE. Lactobacilli and the normal human anaerobic microflora. *Clinical Infectious Diseases*. 1993;16(Supplement4):S181-7.
- 7- Amabebe E, Anumba DOC. The vaginal microenvironment: the physiologic role of Lactobacilli. *Front Med (Lausanne)*. 2018;5:181.
- 8- Wathne B, Holst E, Hovelius B, Mårdh PA. Vaginal discharge-comparison of clinical, laboratory and microbiological findings. *Acta obstetrica et gynecologica Scandinavica*. 1994;73(10):802-8.
- 9- Hoffman, Barbara ,Schorge, John,Schaffer, Joseph, Halvorson, Lisa ,Bradshaw, Karen ,Cunningham, F.Williams *Gynecology*, Second Edition. McGraw Hill Professional. 2012.
- 10-Hacker NF, Gambone JC, Hobel CJ. Hacker & Moore's essentials of obstetrics and gynecology. Elsevier Health Sciences; 2015
- 11- Hillier SL, Holmes KK, Sparling PF, Mardh P A,Lemon SM, Stamm WA, et al. Bacterial vaginosis.*Sex Transm Dis*. 1999; 5: 58-63.
- 12- Paladine HL and Desai UA. Vaginitis: diagnosis and treatment. *Am Fam Physician*.2018 ; 9(5): 97-321.
- 13-Fredricks DN, Fiedler TL, Thomas KK, Oakley BB, Marrazzo JM. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. *Journal of clinical microbiology*. 2007;45(10):3270-6.
- 14-Kalra A, Palcu CT, Sobel JD, Akins RA. Bacterial vaginosis: culture-and PCR-based characterizations of a complex polymicrobial disease's pathobiology. *Current infectious disease reports*. 2007;9(6):485-500.
- 15- Workowski KA. Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. *Clinical Infectious Diseases*. 2015;61(suppl 8): 759-62.
- 16-Keane F, Ison CA, Noble H, Estcourt C"Bacterial vaginosis". *Sex Transm Infect*. 2006;82 Suppl 4: 16–8.
- 17-Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in non - pregnant women. *Cochrane Database of Systematic Reviews*. 2009; 8 (3):CD006055
- 18-Swidsinski A , Loening-Baucke V , Mendling W, Dorffel Y ,Schilling J, Halwani Z, et al. Infection through structured polymicrobial Gardnerella biofilms (StPM-GB). *Histopathol*. 2014; 29: 567–587.
- 19-Patterson JL, Stull-Lane A, Girerd PH, Jefferson KK. Analysis of adherence, biofilm formation and cytotoxicity suggests a greater virulence potential of Gardnerella vaginalis relative to other bacterial-vaginosis-associated anaerobes. *Microbiology*. 2010;156:392.
- 20- Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, et al. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. *American journal of obstetrics and gynecology*. 2001 Aug 1;185(2):363-9.
- 21-Chen HM, Chang TH, Lin FM, Liang C, Chiu CM, Yang TL, Yang T, Huang CY, Cheng YN, Chang YA, Chang PY. Vaginal microbiome variances in sample groups categorized by clinical criteria of bacterial vaginosis. *BMC genomics*. 2018;19(10):167-78.
- 22- Patterson JL, Girerd PH, Karjane NW, Jefferson KK. Effect of biofilm phenotype on resistance of Gardnerella vaginalis to hydrogen peroxide and lactic acid. *American journal of obstetrics and gynecology*. 2007;197(2):170.
- 23-Alves P, Castro J, Sousa C, Cereija TB, Cerca N. Gardnerella vaginalis outcompetes 29 other bacterial species isolated from patients with bacterial vaginosis, using in an in vitro biofilm formation model. *The Journal of infectious diseases*. 2014; 210(4):593-6.
- 24-Swidsinski A, Loening-Baucke V, Swidsinski S, Verstraelen H. Polymicrobial. Gardnerella biofilm resists repeated intravaginal antiseptic treatment in a subset of women with bacterial vaginosis: a preliminary report. *Archives of gynecology and obstetrics*. 2015;291(3):605-9.
- 25-Machado A, Salgueiro D, Harwich M, Jefferson KK, Cerca N. Quantitative analysis of initial adhesion of bacterial vaginosis-associated anaerobes to ME-180 cells. *Anaerobe*. 2013;23:1-4.
- 26-Mendling W, Palmeira-de-Oliveira A, Biber S, Prasauskas V. An update on the role of Atopobium vaginae in bacterial vaginosis: what to consider when choosing a treatment? A mini review. *Archives of gynecology and obstetrics*. 2019:1-6.
- 27-Weissenbacher ER, Donders G, Unzeitig V, De Tejada BM, Gerber S, et al. A comparison of dequalinium chloride vaginal tablets (Fluomizin®) and clindamycin vaginal cream in the treatment of bacterial vaginosis: a single-blind, randomized clinical trial of efficacy and safety. *Gynecologic and obstetric investigation*. 2012;73(1):8-15.
- 28-Muzny CA, Blanchard E, Taylor CM, Aaron KJ, Talluri R, Griswold ME, Redden DT, Luo M, Welsh DA, Van Der Pol WJ, Lefkowitz EJ. Identification of key bacteria involved in the induction of incident bacterial vaginosis: a prospective study. *The Journal of infectious diseases*. 2018;218(6):966-78.
- 29-Petrova MI, Reid G, Vanechoutte M, Lebeer S. Lactobacillus iners: friend or foe?. *Trends in microbiology*. 2017; 25(3):182-91.
- 30-Macklaim JM, Fernandes AD, Di Bella JM, Hammond JA, Reid G, Gloor GB. Comparative meta-RNA-seq of the vaginal microbiota and differential expression by Lactobacillus iners in health and dysbiosis. *Microbiome*. 2013; 1(1):1-1.
- 31-Bautista CT, Wurapa EK, Saterren WB, Morris SM, Hollingsworth BP, Sanchez JL. Association of bacterial vaginosis w women in the US Army. *American journal of preventive medicine*. 2017; 52(5):632-9.
- 32-Hong KH, Hong SK, Im Cho S, Ra E, Han KH, Kang SB, Kim EC, Park SS, Seong MW. Analysis of the vaginal microbiome by next-generation sequencing and evaluation of its performance as a clinical diagnostic tool in vaginitis. *Annals of laboratory medicine*. 2016; 36(5):441.

- 33-Antonucci F, Mir W, Fontana C. Comparison between Nugent's and Hay/Ison scoring criteria for the diagnosis of bacterial vaginosis in WASP prepared vaginal samples. *Clinical Investigation*. 2017;7(3):89-93.
- 34-Mohammadzadeh F, Dolatian M, Jorjani M, Majd HA. Diagnostic value of Amsel's clinical criteria for diagnosis of bacterial vaginosis. *Global journal of health science*. 2015;7(3):8.
- 35- Castro J, Machado D, Cerca N. Unveiling the role of *Gardnerella vaginalis* in polymicrobial bacterial vaginosis biofilms: the impact of other vaginal pathogens living as neighbors. *The ISME journal*. 2019;13(5):1306-17.
- 36- Hardy L, Jaspers V, Abdellati S, De Baetselier I, Mwambarangwe L, Musengamana V, van de Wijgert J, Vanechoutte M, Crucitti T. A fruitful alliance: the synergy between *Atopobium vaginae* and *Gardnerella vaginalis* in bacterial vaginosis-associated biofilm. *Sexually transmitted infections*. 2016; 92(7):487-91.
- 37-Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, Reed BD, Summers PR. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *American journal of obstetrics and gynecology*. 1998; 178(2):203-11.
- 38-Nduba V, Mwachari C, Magaret A, Park DR, Kigo A, Thomas M, Hooton, MD. *Proc Natl Acad Sci US A*. 2006;103:5977-82.
- 39-Hainer BL, Gibson MV. Vaginitis: diagnosis and treatment. *American family physician*. 2011; 83(7):807-15.
- 40-Usatine R, Smith MA, Mayeaux EJ, Chumley H. *Color Atlas of Family Medicine* (2nd ed.). New York: McGraw Hill. 2013. 23pp
- 41-Paladine HL, Desai UA. Vaginitis: diagnosis and treatment. *Am Fam Physician*. 2018;97(5):321-9.
- 42-Achkar JM, Fries BC. *Candida* infections of the genitourinary tract. *Clin Microbiol Rev*. 2010;23(2):253-73.
- 43-Sobel, JD . "Vulvovaginal candidosis". *Lancet*. 2007; 369(9577): 1961-71.
- 44-Rebecca Jeanmonod , Donald Jeanmonod. *Vaginal Candidiasis*. NCBI. 2020 USA.
- 45-Mba IE, Nweze EI. Mechanism of *Candida* pathogenesis: revisiting the vital drivers. *European Journal of Clinical Microbiology & Infectious Diseases*. 2020;39:1797-819.
- 46-Lowe NK, Neal JL, Ryan - Wenger NA. Accuracy of the clinical diagnosis of vaginitis compared with a DNA probe laboratory standard. *Obstet Gynecol*. 2009; 113: 89 - 95.
- 47-Vulvovaginal Candidiasis . *STD Treatment Guidelines*. 2015 .
- 48- Lowe NK, Neal JL, Ryan-Wenger NA. Accuracy of the clinical diagnosis of vaginitis compared to a DNA probe laboratory standard. *Obstetrics and gynecology*. 2009;113(1):89.
- 49-Ilkit M, Guzel AB. The epidemiology, pathogenesis, and diagnosis of vulvovaginal candidosis: a mycological perspective. *Critical reviews in microbiology*. 2011; 37(3):250-61.
- 50-Mendling W. Guideline: vulvovaginal candidosis (AWMF 015/072), S2k (excluding chronic mucocutaneous candidosis). *Mycoses*. 2015;58:1-5.
- 51- das Neves J, Pinto E, Teixeira B, Dias G, Rocha P, Cunha T, et al. Local treatment of vulvovaginal candidosis. *Drugs*. 2008;68(13):1787-802.
- 52- Müller J, Nold B, Kubitzka D, Baumert J. Quantitative Untersuchungen über die Döderlein - Flora gesunder sowie mykosekranker Probandinnen unter lokaler Isoconazol - Nitrat - Therapie. In: Seeliger HPR (ed) *Gyno - Travogen, Monographie Excerpta Medica*. Amsterdam: Oxford Princeton. 1981: 81-93.
- 53-Pappas PG, Kauffman CA, Andes DR, Clark CJ, Marr KA, Ostrosky-Zeichner L. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of Society of America. *Clin Infect Dis* .2016;62:e1-50.
- 54-Johnston VJ, "Global epidemiology and control of *Trichomonas vaginalis*". *Current Opinion in Infectious Diseases*. Mabey DC (2008).
- 55- Lindmark DG, Müller M. Hydrogenosome, a Cytoplasmic Organelle of the Anaerobic Flagellate *Trichomonas foetus*, and Its Role in Pyruvate Metabolism. *J Biol Chem*. 1973; 248(22): 7724-8.
- 56- Conrad MD, Bradic M, Warring SD, et al. Getting trichy: Tools and approaches to interrogating *Trichomonas vaginalis* in a post-genome world. *Trends Parasitol*. 2013; 29(1): 17-25.
- 57- Bradic M, Carlton JM. Does the common sexually transmitted parasite *Trichomonas vaginalis* have sex? .*PLoS Pathog*. 2018; 14(3): e1006831.
58. Beri D, Yadav P, Devi HRN, et al. Demonstration and Characterization of Cyst-Like Structures in the Life Cycle of *Trichomonas vaginalis*. *Front Cell Infect Microbiol*. 2019; 9: 430
- 59- James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018; 392(10159):1789-858.
- 60-Paladine HL, Desai UA. Vaginitis: diagnosis and treatment. *Am Fam Physician*. 2018; 97(5):321-9.
- 61-Mendling W. Guideline: vulvovaginal candidosis (AWMF 015/072), S2k (excluding chronic mucocutaneous candidosis). *Mycoses*. 2015;58:1-5.
- 62- Dewi J de-W, Jan H D, Sander O, Remco PHP, Servaas AM. Prevalence of *Trichomonas vaginalis* infection and protozoan load in South African women: a cross-sectional study. *BMJ*. 2017;7:e016959

- 63- Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci*. 2011; 108 (Suppl 1): 4680–7.
- 64- Brotman RM, Bradford LL, Conrad M, et al. Association between *Trichomonas vaginalis* and vaginal bacterial community composition among reproductive age women. *Sex Transm Dis*. 2012; 39(10): 807–12.
- 65- Jarrett OD, Srinivasan S, Richardson BA, et al. Specific Vaginal Bacteria Are Associated With an Increased Risk of *Trichomonas vaginalis* Acquisition in Women. *J Infect Dis*. 2019; 220(9): 1503–10.
- 66-Hinderfeld AS, Simoes-Barbosa A. Vaginal dysbiotic bacteria act as pathobionts of the protozoal pathogen *Trichomonas vaginalis*. *Microb Pathog*. 2020; 138: 103820.
- 67- Hinderfeld AS, Phukan N, Bär AK, et al. Cooperative Interactions between *Trichomonas vaginalis* and Associated Bacteria Enhance Paracellular Permeability of the Cervicovaginal Epithelium by Dysregulating Tight Junctions. *Infect Immun*. 2019; 87(5): e00141–19.
- 68- Phukan N, Brooks AES, Simoes-Barbosa A. A Cell Surface Aggregation Promoting Factor from *Lactobacillus gasseri* Contributes to Inhibition of *Trichomonas vaginalis* Adhesion to Human Vaginal Ectocervical Cells. *Infect Immun*. 2018; 86(8): e00907-17.
- 69- Pinheiro J, Biboy J, Vollmer W, et al. The Protozoan *Trichomonas vaginalis* Targets Bacteria with Laterally Acquired NlpC/P60 Peptidoglycan Hydrolases. *MBio*. 2018; 9(6): e01784–18.
- 70-Schwebke JR, Burgess D. Trichomoniasis. *Clin Microbiol Rev*. 2004; 17(4):794-803.
- 71-Forna F, Gülmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane Database Syst Rev*. 2003;2: CD000218.
- 72- Sherrard J, Ison C, Moody J et al. United Kingdom national guideline on the management of *Trichomonas vaginalis* 2014. *Int J STD AIDS*.2014;25:541–549.
- 73- Bickley LS, Krisher KK, Punsalang A et al. Comparison of direct fluorescent antibody, acridine orange, wet mount and culture for detection of *Trichomonas vaginalis* in women attending a public sexually transmitted disease clinic. *Sex Trans Dis* .1989;127–131.
- 74-Munson E, Napierala M, Olson R et al. Impact of *Trichomonas vaginalis* transcription-mediated amplification-based analyte-specific reagent testing in a metropolitan setting of high sexually transmitted disease prevalence. *J Clin Microbiol*. 2008;46:3368–3374.
- 75- Cosentino LA, Campbell T, Jett A et al. Use of nucleic acid amplification testing or diagnosis of anorectal sexually transmitted infections. *J Clin Microbiol*. 2012;50:2005–2008.
- 76- Schwebke JR, Hobbs MM, Taylor SN and et al. Molecular testing for *Trichomonas vaginalis* in women: results from a prospective US clinical trial. *J Clin Microbiol*. 2011;49(12):4106–4111.
- 77-Ginocchio CC, Chapin K, Smith JS et al. Prevalence of *Trichomonas vaginalis* and coinfection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the United States as determined by the Aptima *Trichomonas vaginalis* nucleic acid amplification assay. *J Clin Microbiol*.2012;50(8):2601–2608.
- 78- Richard H A, Rita O A, Noah O-N, Harriet B, Georgina A-M ,et al. *Trichomonas vaginalis* infection and the diagnostic significance of detection tests among Ghanaian outpatients. *BMC Womens Health*. 2018; 18: 206.
- 79- Leitsch D: A review on metronidazole. An old warhorse in antimicrobial chemotherapy. *Parasitology*. 2019; 146(9): 1167–78.
- 80-Kissinger P, Muzny CA, Mena LA, et al. Single-dose versus 7-day-dose metronidazole for the treatment of trichomoniasis in women: An open-label, randomised controlled trial. *Lancet Infect Dis*. 2018; 18(11): 1251–1259.
- 81- Mandalapu D, Kushwaha B, Gupta S, et al. 2-Methyl-4/5-nitroimidazole derivatives potentiated against sexually transmitted *Trichomonas*: Design, synthesis, biology and 3D-QSAR study. *Eur J Med Chem*. 2016; 124: 820–39.
- 82- Jarrad AM, Debnath A, Miyamoto Y, et al. Nitroimidazole carboxamides as antiparasitic agents targeting *Giardia lamblia*, *Entamoeba histolytica* and *Trichomonas vaginalis*. *Eur J Med Chem*. 2016; 120: 353–62.