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AMPATHCHAT

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The aetiology, diagnosis and management of the vaginal discharge syndrome

Introduction

The vaginal discharge syndrome may be secondary to vulvovaginitis or cervicitis. Both of these conditions have infectious and non-infectious aetiologies. Vulvovaginitis is a common condition and most women will have at least one episode per lifetime, making it one of the most common gynaecological conditions. Of women presenting with vaginitis, approximately 70–90% will present with one of the following infectious aetiologies: bacterial vaginosis (40–50%), vulvovaginal candidiasis (20–25%) or trichomoniasis (15–20%). Non-infectious aetiologies occur less commonly (approximately 5–10% of cases) and include atrophic vaginitis, desquamative inflammatory vaginitis, retention of foreign bodies, irritants and allergens. Cervicitis, commonly secondary to sexually transmitted infections, may also present with vaginal discharge in symptomatic females.

Aetiology

Table 1 summarises the most common causes of the genital discharge syndrome in terms of pathogenesis, symptoms and signs, as well as useful point-of-care testing strategies that may aid in establishing an aetiological diagnosis.

Table 1: Aetiology, signs and symptoms and commonly available point-of-care testing available for the diagnosis of vaginitis

Condition	Pathogenesis	Symptoms and signs	Microscopy (saline wet mount, unless stated otherwise)	Vaginal pH level	Whiff test
Normal vaginal secretions	None	Odourless. Pruritis and inflammation absent.	Squamous epithelial cells, rare leukocytes, Lactobacilli predominant.	4–4.5	Negative
Bacterial vaginosis (BV)	Altered vaginal microbiota.	Thin, homogenous, fishy-smelling grey discharge.	≥20% of epithelial cells are clue cells. Absent/ few lactobacilli. Few or no leukocytes present.	>4.5	Positive
Vulvovaginal candidiasis (VVC)	Infection with *Candida* species.	Thick, white, adherent cottage cheese discharge. Vulvar erythema and pruritis.	Budding yeasts or mycelia on saline and KOH wet mount in approximately 70% of patients.	4–4.5	Negative
Trichomoniasis	STI: *Trichomonas vaginalis.*	Purulent discharge. Vulvar irritation. Dysuria. Dyspareunia.	Numerous leukocytes and motile flagellated trichomonads in approximately 60% of patients.	>4.5	Often positive
Desquamative inflammatory vaginitis	Uncertain.	Purulent vaginal discharge. Vulvar irritation, dysuria and dyspareunia.	Numerous leukocytes. Immature parabasal cells on saline wet mount.	>4.5	Negative
Oestrogen deficiency	Due to oestrogen deficiency.	Vaginal dryness, burning, irritation, dyspareunia, bleeding, discharge.	Immature parabasal cells. With or without leukocytes.	>4.5	Negative
Cervicitis: Infectious	Main pathogens: *N. gonorrhoeae, C. trachomatis* and *M. genitalium.*	Purulent discharge. Dysuria, lower abdominal pain and dyspareunia.	Numerous leukocytes. Mature vaginal cells.	May be elevated	Negative
Cervicitis: non-infectious	Mechanical or chemical irritation resulting in an inflamed ectropion.	Purulent discharge. No vulvar discomfort, dysuria or dyspareunia. ± post-coital bleeding.	Numerous leukocytes. Mature vaginal cells.	May be elevated	Negative

Bacterial vaginosis (BV) is a clinical condition caused by a shift in the vaginal microbiota from the normally predominant hydrogen peroxide-producing *Lactobacillus* species to a more diverse community of anaerobic and facultative bacteria with overgrowth of *Gardnerella vaginalis* playing a key role in the development of BV. This state of dysbiosis results in an increase in vaginal pH and amine production, resulting in the typical clinical presentation of a thin, grey, homogeneous discharge with a fishy odour. Furthermore, patients with BV are at higher risk of the acquisition of sexually transmitted infections, including HIV, pelvic inflammatory disease (PID) and poor reproductive outcomes, such as pre-term delivery.

Vulvovaginal candidiasis (VVC) is caused by overgrowth of *Candida* species in the vagina. *Candida albicans* is most commonly implicated, but non-albicans species may also be causative. Most patients present with uncomplicated sporadic disease. Candida vulvovaginitis is considered to be complicated in the following settings: immune-compromised patients (HIV positive, diabetic, malignancy, immuno-supressive drugs), pregnant patients, patients with frequent recurrences, severe disease or those who are infected with non-albicans *Candida species*. This classification is important as the treatment differs between the two groups.

Trichomoniasis is caused by the flagellated protozoan *Trichomonas vaginalis* and is considered a sexually transmitted infection (STI). Although evidence points to a role for sexual transmission in both BV and VVC, these conditions are not currently regarded as true STIs and the treatment of sexual partners is not routinely recommended.

Neisseria gonorrhoeae, *Chlamydia trachomatis* and *Mycoplasma genitalium* are known causes of gonococcal- and non-gonococcal urethritis in males and cervicitis in females. Females may present with a vaginal discharge, but a significant proportion of patients may be asymptomatic. Antibiotic resistance is an emergent problem in these pathogens. The other *Mycoplasma* and *Ureaplasma* species (*M. hominis, U. urealyticum* and *U. parvum*) are colonisers of the male and female genital tract and their role in urethritis and the vaginal discharge syndrome is unclear. However, they are linked to bacterial vaginosis and poor reproductive outcomes in pregnant females.

Diagnosis

The initial clinical evaluation, including history, physical examination, pH, wet mount microscopy and whiff test of vaginal secretions, can diagnose a significant proportion of BV, VVC and trichomoniasis cases. Amsel's criteria, which are used for the diagnosis of BV, are listed in Table 2. To establish a diagnosis of BV, three or more of these criteria need to be positive. When compared to Gram stain, Amsel's criteria is 90% sensitive and 77% specific.

Gram stain of the vaginal discharge is currently regarded as the gold standard for the diagnosis of BV. The Nugent score and Hay/Ison criteria are two Gram stain techniques based on bacterial morphology for the diagnosis of BV. When compared to clinical criteria, the sensitivity ranges from 62–100%. These are laboratory-based diagnostic techniques that need to be performed by skilled personnel. Furthermore, some bacteria that are associated with BV display morphological variation or poor Gram staining, thereby decreasing the sensitivity and specificity of the above techniques.

Commercially available molecular platforms are emerging as promising diagnostic modalities for the diagnosis of BV. These assays typically detect and quantify *G. vaginalis* or quantify the ratio between beneficial *Lactobacillus* sp. and BV-associated bacteria; in essence, a molecular Nugent score without the above limitations associated with Gram stain. Molecular diagnostic tests for BV are objective, can detect fastidious bacteria, enable quantification and can be performed on self-collected vaginal swabs. Currently, the cost of these assays is the main limiting factor and they are not employed as part of the routine diagnostic work-up of vaginitis and may be more appropriately used in the setting of recurrent vaginitis or where Nugent scoring or point-of-care testing is indeterminate.

Saline wet mount identifies *Candida* spp. (hyphae on wet mount) in approximately 50–70% of cases. The addition of KOH may marginally increase sensitivity. A culture of vaginal swabs or secretions remains the gold standard for the diagnosis of VVC. In addition, species identification and susceptibility testing can also be performed if indicated. Similarly, approximately 60% of cases of trichomoniasis can be diagnosed by observing motile trichomonads in saline wet mount if the wet mount is examined within 10 to 20 minutes of taking the sample. Molecular-based testing (PCR) remains the gold standard for diagnosing trichomoniasis.

Neisseria gonorrhoeae, *C. trachomatis* and *M. genitalium are* fastidious organisms and molecular testing of urine, urethral and cervical swabs has become the mainstay of diagnosis. Ideally, specimens submitted for culture and susceptibility testing of *N. gonorrhoeae* should be transported to the lab in specialised transport media.

Ampath currently offers microscopy (which includes Nugent scoring) and culture of vaginal swabs that can be requested if BV, trichomoniasis, VVC or gonorrhoea is suspected. The benefits of culture include the ability to perform antimicrobial susceptibility testing of *N. gonorrhoeae*, as well as species-level identification of *Candida*. Ampath also offers the following two molecular tests: a BV PCR, which is a multiplex test detecting BV, *T. vaginalis* and *Candida* species, as well as a multiplex STI PCR for the detection of *N. gonorrhoeae*, *C. trachomatis, M. genitalium* and *T. vaginalis*. Molecular testing remains the most sensitive modality for the detection of *N. gonorrhoeae* and *T. vaginalis*. *Chlamydia trachomatis* and *M. genitalium* can only be detected by PCR testing in the routine diagnostic laboratory.

Table 2: Amsel's criteria

Three or more positive criteria are considered positive for BV
• Homogenous, thin, grey discharge coating vaginal wall • Vaginal pH >4.5 • Positive whiff amine test (fishy odour when 10% KOH is added to vaginal discharge) • Clue cells on saline wet mount (at least 20% of epithelial cells)

Management

The South African Department of Health has opted for a syndromic approach to the management of STIs, including the vaginal discharge syndrome, as outlined in the 2015 sexually transmitted infections guidelines (available at: http://www.nicd.ac.za/assets/files/STIguidelines3-31-15(cmyk).pdf). These guidelines simplify the management, allow for treatment at the same visit, cut out laboratory costs and allow for the management of mixed infections. However, this syndromic management approach, as outlined in the current version of the guidelines, has many pitfalls. It often leads to misdiagnosis and inappropriate therapy, which further disturbs the vaginal microbiome. In addition, the current treatment recommendations are sub-optimal for the management of BV, *T. vaginalis* and *M. genitalium* infections. Diagnostic testing enables targeted treatment, increases therapeutic compliance, and facilitates better management of recurring cases. Where resources are available, a rational, cost-effective approach to the diagnosis of STIs , BV and *T. vaginalis* should be taken.

The management of the most common causes of infectious vaginitis is outlined in Table 3. The choice between topical and oral therapy for BV, as outlined in Table 3, is based on patient preference, as both regimens are equally effective.

However, oral treatment regimens are preferred in pregnancy. Clindamycin 300 mg po bid for 7 days is an acceptable alternative to oral metronidazole treatment. The 2 g single dose of metronidazole, as outlined in the South African syndromic management guidelines, is known to be associated with lower cure rates for both *T. vaginalis* and BV.

The management of complicated and uncomplicated VVC is briefly described in Table 3. For non-albicans *Candida* species, treatment depends on the species identified. Treatment options for *C. glabrata* are boric acid vaginal capsules and, alternatively, topical flucytosine cream. Topical clotrimazole or miconazole for 7 to 14 days can be used in cases of *C. krusei* infection.

Antibiotic resistance is an emergent problem, especially with *N. gonorrhoeae* and *M. genitalium*. The single 1 g dose of azithromycin forming part of syndromic management results in cure in only approximately 67% of cases of confirmed *M. genitalium* infections and may also select for resistant strains of *M. genitalium,* hence a five-day course of azithromycin is currently recommended as primary regimen for confirmed cases of *M. genitalium* infection. Moxifloxacin should be used in cases of azithromycin resistant and complicated *M. genitalium* infections.

Table 3: Treatment regimens for the most common causes of vaginitis

Primary treatment regimen	Pregnancy	Recurrent/complicated disease
Bacterial vaginosis **Systemic:** Metronidazole 400 mg bid po x 7 days. **Topical:** Metronidazole vaginal gel x 5 days **or** 2% clindamycin vaginal cream x 7 days applied at bedtime.	Same as for non-pregnant. Oral therapy may have the added advantage of treating subclinical upper genital tract infection.	**First recurrence:** Retreat with same regimen. **Multiple recurrences:** Metronidazole vaginal gel twice weekly for 4–6 months **or** Metronidazole 400 mg bid po x 7 days followed by boric acid gelatin capsules 600 mg intravaginally x 21 days, then Metronidazole vaginal gel: one applicator (5 g) at bedtime twice a week for 16 weeks.
Vulvovaginal candidiasis **Systemic:** Fluconazole 150 mg po as single dose. **Topical:** Topical azole therapy.	Topical azole therapy for 7 days.	**Immunocompromised host:** Fluconazole 150 mg po dly **or** topical azole therapy 7–14 days. **Recurrent VVC[a]:** Fluconazole 150 mg every 72 hours po for 3 doses, followed by fluconazole 150 mg po weekly for six months. If not feasible, topical azole for 10–14 days, followed by six months of topical maintenance. **Severe VVC[b]:** Topical azole for 7–14 days **or** fluconazole 150 mg every 72 hours po for 2–3 doses, depending on severity. **Non-albicans VVC:** Therapy depends on species identified. Please consult a microbiologist.
Trichomoniasis Metronidazole 400 mg po bid for 7 days[c].	Metronidazole 400 mg po bid for 7 days.	Differentiate persistent or recurrent infection from reinfection. **First recurrence:** Metronidazole 400 mg bid po x 7 days. **Second recurrence:** Metronidazole 2 g po daily for 7 days.
Cervicitis Treat for *C. trachomatis* and *N. gonorrhoeae* if at high risk for STI,[c,d]: Ceftriaxone 250 mg imi + azithromycin 1g po STAT. If at low risk for STI, defer treatment while awaiting results of diagnostic work-up.	Same as for non-pregnant women (avoid doxycycline).	Recurrence needs to be distinguished from reinfection. If recurrence or treatment failure, confirm aetiology by means of PCR testing, as well as culture and susceptibility testing in cases of *N. gonorrhoeae*. For confirmed *M. genitalium* infection: • Azithromycin 500mg p.o on day 1, then 250 mg p.o dly on day 2 to day 5 in uncomplicated cases. • Alternative regimen: Moxifloxacin 400 mg p.o dly for 10 to 14 days if macrolide resistance is suspected or confirmed.

[a] Recurrent VVC : ≥ four episodes of symptomatic VVC within one year
[b] Severe VVC: Extensive vulvar erythema, oedema, excoriation, and fissure formation
[c] Treatment of sexual partners indicated
[d] In case of positive test for STI: treat specific aetiological agent and retest three months after treatment because of high rates of reinfection

Conclusion

The vaginal discharge syndrome occurs commonly. Bacterial vaginosis, VVC and trichomoniasis are the most common causes among women of child-bearing age. Clinical presentation, history, saline and potassium hydroxide wet mount and pH testing are reasonably sensitive and cost-effective diagnostic strategies, which can be performed at the point of care to diagnose the above conditions.

Where these tests are not available or inconclusive, laboratory tests, such as Nugent scoring and PCR, are also available. Cervicitis due to the sexually transmitted pathogens *N. gonorrhoeae*, *C. trachomatis* and the emerging pathogen *M. genitalium* may also manifest as a vaginal discharge in symptomatic females. Establishing an aetiological diagnosis as opposed to employing syndromic management enables optimal targeted treatment from the outset.

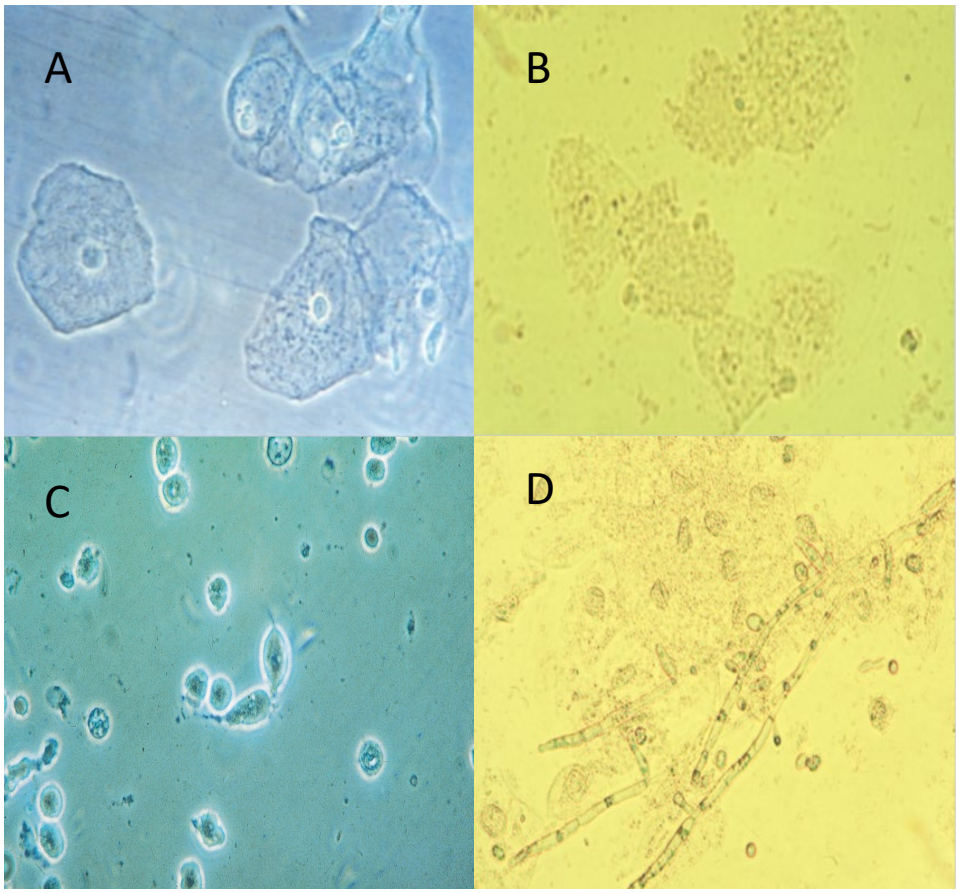

Figure 1: Saline wet mounts of vaginal secretions displaying the following: A) Normal vaginal secretions with epithelial cells and predominantly lactobacilli. B) Clue cells – note vaginal epithelial cells coated in bacteria and absence of rods typical of BV. C)Flagellated trichomonads and leukocytes as seen in trichomoniasis. D) Hyphae observed on wet mount as seen in VVC . Figures obtained form: Mandell, Douglas and Bennett's Principles and practice of infectious diseases, 9 th edition, 2019

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