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Recent advances in vulvovaginal Candidiasis research: A narrative review

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Abstract

Vulvovaginal Candidiasis (VVC) is a significant public health concern, and current article focuses primarily on understanding this infection's molecular processes. The hosts defence mechanisms and their dysregulation, such as the innate immune response and the genetic susceptibility factors, play a crucial role in determining the susceptibility to VVC. *Candida*-host interactions in the vaginal environment, including the adhesion mechanisms and the tissue invasion, have been extensively investigated, revealing the intricate strategies employed by *Candida* spp. to colonize and persist in the human host. Moreover, the virulence factors secreted by *Candida* spp., such as the hydrolytic enzymes and toxins, contribute to the tissue damage and modulation of the immune response, aiding in *Candida* spp. survival and evasion of the host defences. The formation of *Candida* biofilms and the complex structures, which are composed of fungal cells encased in an extracellular matrix, has emerged as an essential aspect of VVC pathogenesis. Biofilms confer *Candida* spp. enhanced resistance to the antifungal agents, leading to treatment challenges and recurrent infections. Advancements in the various diagnostic techniques have also played a pivotal role in VVC research. Molecular diagnostics, next-generation sequencing, and proteomic approaches offer improved accuracy and rapid identification of *Candida* spp., enabling precise diagnosis and personalized treatment strategies. Such techniques are significant for developing novel therapeutic targets, including disrupting the adhesion mechanisms, inhibiting the virulence factor production, and targeting biofilm formation. These advances hold promise for developing more effective preventive strategies, therapeutic interventions, and improved diagnostic tools. Overall, this review article

aimed to discuss the recent research that provides valuable insights into the infection mechanisms driving the vulvovaginal Candidiasis and their diagnosis, ultimately improving the quality of life for the women affected by this disease.

Keywords: Vulvovaginal Candidiasis, Infection mechanism, Molecular diagnostics, Preventive strategies, Alternative therapies

1. Introduction

Vulvovaginal Candidiasis (VVC) is a common fungal infection affecting women worldwide, primarily caused by *Candida* spp. Up to 75 % of the women will experience at least one episode of VVC during their lifetime, with significant numbers experiencing recurrent infections (Willems *et al*., 2020). The VVC condition is characterized by several symptoms, including vaginal itching, burning, abnormal discharge, and discomfort, which can significantly affect the individual's quality of life and overall well-being (Sustr *et al*., 2020). Recently, significant advances have been made in understanding the molecular mechanisms underlying VVC pathogenesis. These breakthroughs have been driven by various technological advancements, such as genomics, proteomics, and metabolomics, thus enabling the researchers to unravel the intricate interplay between *Candida* spp. and the vaginal environment (Jeanmonod and Jeanmonod, 2022).

The host response plays a critical role in determining the susceptibility to VVC. Recent studies have shed light on the dysregulation of innate immune defences and the impact of genetic factors on VVC susceptibility (Czechowicz *et al*., 2022). *Candida*-host interactions, including adhesion mechanisms, tissue invasion, and formation of biofilms, have also been extensively investigated, revealing the complex strategies that *Candida* spp. employ to colonize and persist in the vaginal environment (Rodriguez-Cerderia *et al*., 2020). Furthermore, the production of virulence factors by *Candida* spp., such as the hydrolytic enzymes and toxins, has been implicated in tissue damage, immune modulation, and evasion of the host immune defences. These virulence factors contribute to the pathogenesis of VVC and provide potential targets for the therapeutic interventions (Kumari *et al*., 2021).

2. Current scenario of vulvovaginal Candidiasis

2.1. Epidemiology and risk factors

Candida albicans and certain non-albicans species, including *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. dubliniensis*, *C. africana*, *C. duobushaemulonii*, and *C. auris* generally cause VVC. The exact prevalence of VVC varies among the different populations, but it is influenced by many factors, including age, reproductive status, sexual activity, antibiotic use, and the underlying medical conditions. Hormonal changes, such as those occurring during pregnancy or in women using oral contraceptives, have been identified as risk factors for VVC. The other risk factors include uncontrolled diabetes, weakened immune system, and the use of broad-spectrum antibiotics. Understanding the epidemiology and risk factors associated with VVC is crucial for effective prevention and management strategies (Sardi *et al*., 2021).

2.2. Clinical manifestations and symptomatology

A range of clinical manifestations and symptoms characterizes VVC. The most common symptom is vaginal itching, often accompanied by a burning sensation. Women may also experience abnormal vaginal discharge, typically thick and white, and resembling cottage cheese. Additionally, redness, swelling, and soreness of the vulva and vaginal tissues may occur (Sustr *et al*., 2020; Willems *et al*., 2020). Some women may experience pain or discomfort

during sexual intercourse or urination. However, it is essential to note that not all women with *Candida* colonization will exhibit these symptoms. The severity and duration of these symptoms can vary among the individuals. Prompt recognition and accurate diagnosis of VVC are essential for appropriate treatment and symptoms relief (Sustr *et al*., 2020; Willems *et al*., 2020; Farr *et al*., 2021; Jeanmonod and Jeanmonod, 2022).

2.3. Recurrent vulvovaginal Candidiasis (RVVC) and its challenges

Recurrent vulvovaginal Candidiasis (RVVC) refers to at least four episodes of VVC within one year (McKloud *et al*., 2021). RVVC challenges the management and quality of life of the affected individuals. The exact mechanisms underlying RVVC are not fully understood, but they may involve several factors, such as persistent *Candida* colonization, immune dysregulation, genetic predisposition, and formation of *Candida* biofilms. RVVC may be challenging to treat, as it often requires long-term or prophylactic antifungal therapy, which may lead to side effects and the development of antifungal resistance. The psychological impact and negative quality of life associated with recurrent infections further contribute to the challenges of RVVC management (McKloud *et al*., 2021).

3. Pathogenesis of vulvovaginal Candidiasis

3.1. Host defence mechanisms and susceptibility

3.1.1. Innate immune response in the vaginal environment

The vaginal mucosa possesses innate immune defence mechanisms that protect it against the vulvovaginal Candidiasis (VVC). These defence strategies include antimicrobial peptides, such as defensins and cathelicidins, as well as cytokines and chemokines, which help to regulating the inflammation and recruit of immune cells at the site of infection. Disruption of the delicate balance of the vaginal microbiota or alterations in the immune signaling pathways can impair the innate immune response, thus increasing the susceptibility to VVC (Balakrishnan *et al*., 2022).

3.1.2. Genetic factors influencing susceptibility to VVC

Genetic variations in the essential immune-related genes have been associated with increased susceptibility to VVC. Polymorphisms in genes encoding for pattern recognition receptors, such as Toll-like receptors (*TLRs*) and cytokines including interleukins (ILs), have been implicated in the altered immune responses and increased susceptibility to *Candida* colonization and infection (Davidson *et al*., 2018). Understanding the genetic factors influencing susceptibility to VVC can provide insights into the individual differences in disease susceptibility and aids in developing personalized treatment approaches (Fig. 1).

3.2. *Candida*-host interactions in the vaginal environment

3.2.1. Adhesion mechanisms of *Candida* spp.

Candida spp. employ various adhesion mechanisms to colonize and persist in the vaginal environment. *Candida* cells express adhesins, such as Als proteins and Hwp1, facilitating their attachment to the vaginal epithelial cells. Furthermore, *Candida* biofilms, complex structures composed of fungal cells encased in an extracellular matrix, play a critical role in their adherence and persistence. Biofilms enable *Candida* cells to withstand the host immune responses and resist the antifungal treatments (Sun *et al*., 2023).

3.2.2. Host immune response and inflammation

According to a previous study conducted by Ardizzoni *et al*., (2021), the host immune response in the vaginal environment plays a dual role in VVC. While an inflammatory response is necessary for eliminating the *Candida* cells; however, excessive or dysregulated inflammation may contribute to tissue damage and exacerbate the symptoms. The immune

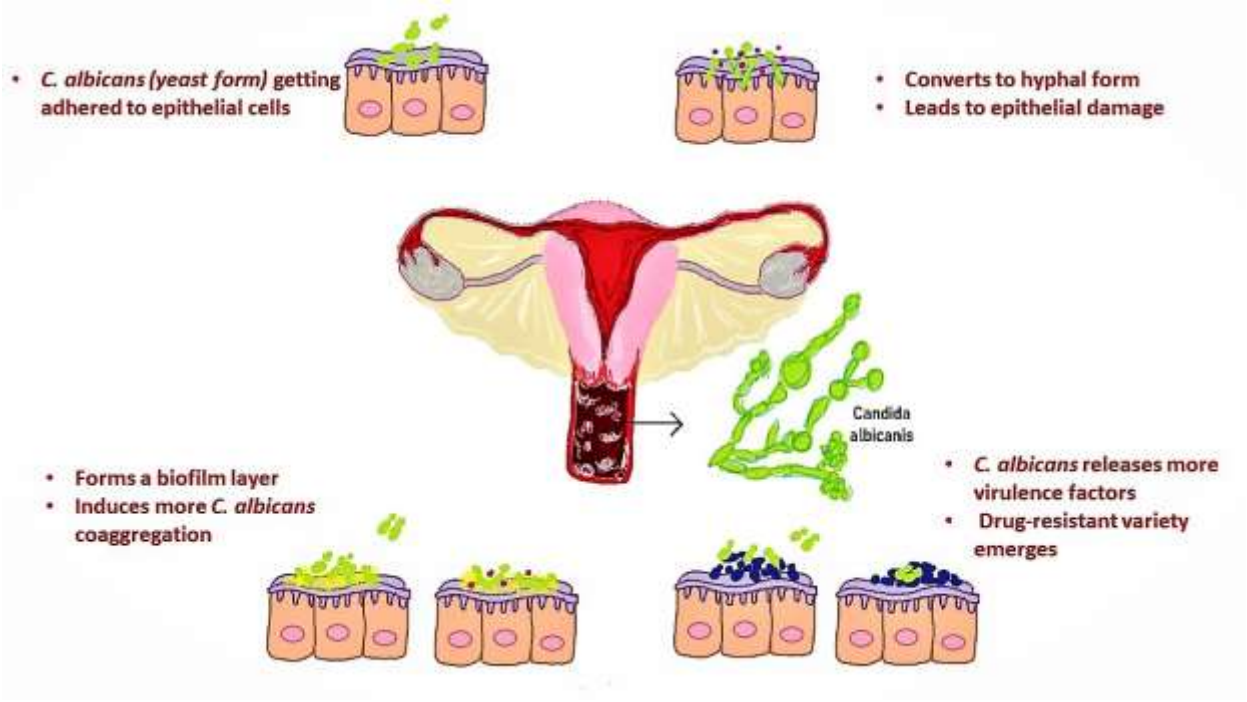

Fig. 1. Infection mechanisms and biofilm formation in vulvovaginal Candidiasis

cells, including the neutrophils, macrophages, and dendritic cells, are recruited at the site of infection, releasing pro-inflammatory cytokines and chemokines. *Candida*-derived factors, including mannans and β-glucans, activate the immune receptors, thus producing inflammatory mediators. Dysregulation of the immune response can lead to recurrent infections and chronic inflammation (Fig. 1).

4. Virulence factors of *Candida* spp.

4.1. Adherence and invasion mechanisms

Candida spp. possess adhesins, such as Als proteins and Hwp1, facilitating their attachment to the vaginal epithelial cells. Adhesins interact with the host cell receptors, promoting adherence and colonization of the vaginal mucosa. Adherence is a critical step in the establishment of an infection. Tissue invasion and damage may occur by hyphae formation, *i.e*., *Candida* spp. can transform from the yeast phase to hyphae, enhancing their invasive capabilities. Hyphae formation allows the *Candida* cells to penetrate the host tissues, leading to a local tissue damage and inflammation. The hyphae can breach the epithelial barriers and invade more profound layers of the vaginal mucosa (Richardson *et al*., 2018). The invasive growth of hyphae contributes to the pathogenicity of *Candida* spp. (Fig. 1).

4.2. Secretion of hydrolytic enzymes

4.2.1. Proteases and their impact on host tissues

A recent study reported by Jacobsen, (2023) revealed that *Candida* spp. produce proteases that

degrade the host proteins, including those involved in the immune defence mechanisms. Proteases can directly damage the host tissues, facilitate tissue invasion, and disrupt the host immune responses, leading to an immune evasion and pathogenesis. Moreover, they contribute to tissue destruction and inflammatory responses.

4.2.2. Phospholipases and their role in membrane disruption

Phospholipases produced by *Candida* spp. can hydrolyse the phospholipids in the host cell membranes. This enzymatic activity allows *Candida* spp. to disrupt the integrity of these cell membranes, facilitating tissue invasion and dissemination. Furthermore, phospholipases can also modulate the host immune responses by affecting the release of the immune mediators (Jacobsen, 2023).

4.3. Toxin production and immune modulation

4.3.1. *Candida* lysin and its effect on the host immune cells

Candida spp. produce *Candida* lysine that is a cytolytic peptide toxin, which can directly damage the host immune cells, including the epithelial cells and the neutrophils. *Candida* lysin induces cell damage, inflammatory responses, and immune cell recruitment, thus contributing to the pathogenesis of *Candida* infections (Moyes *et al*., 2011). In addition, this toxin plays a crucial role in host-Candida interactions and immune evasion.

4.3.2. Modulation of the immune response by *Candida* toxins

A previous report by Netea *et al*., (2015) suggests that *Candida* toxins, such as gliotoxin and *Candida* lysine, can modulate the host immune responses. These toxins interfere with the immune cell's function, disrupt cytokine production, and impair functions of the immune effector cells, leading to an immune suppression or dysregulation. *Candida* spp. can evade the immune clearance and establish persistent infections by manipulating the host immune response (Netea *et al*., 2015).

4.4. Biofilm formation in vulvovaginal Candidiasis

4.4.1. Importance of biofilms in *Candida* infections

Biofilm formation is crucial in VVC pathogenesis. Biofilm-associated VVC is characterized by adherence of *Candida* cells to the vaginal mucosal surfaces, in addition to the formation of complex biofilm communities. Biofilm-associated infections are often more persistent, recurrent, and challenging to treat, compared with those caused by the free-floating *Candida* cells (Fig. 1). Biofilms protect the *Candida* cells from the host immune responses and the antimicrobial agents, contributing to the chronicity and treatment resistance observed in VVC (Wu *et al*., 2020).

4.4.2. Resistance to antifungal treatment in biofilm-forming *Candida* spp.

Biofilm formation enhances the resistance of *Candida* cells to antifungal treatments. The biofilm matrix acts as a physical barrier, limiting the penetration and efficacy of the antifungal agents. Furthermore, *Candida* cells within the biofilms exhibit altered metabolic activity and gene expression profiles, reducing the susceptibility to the antifungal drugs (Cavalheiro and Teixeira, 2018). The presence of biofilms can significantly hinder the successful treatment outcomes in VVC.

4.5. Mechanisms of biofilm formation and maturation

4.5.1. Extracellular matrix production and architecture

Biofilm formation involves the production and secretion of extracellular matrix components by *Candida* cells. This extracellular matrix comprises polysaccharides, proteins, and DNA, which provide structural support to the biofilm community. Moreover, it contributes to the biofilm architecture,

stability, and resistance to the environmental stresses (Cavalheiro and Teixeira, 2018; Wu *et al*., 2020).

4.5.2. Regulatory factors governing biofilm development

Several regulatory factors play essential roles in *Candida* biofilm formation and maturation. These factors include transcriptional regulators, signaling pathways, and environmental cues (Fig. 1). For example, the transcription factor *Bcr1* regulates the gene expression in biofilm development, while the environmental factors such as pH and nutrient availability, affect the biofilm formation (Cavalheiro and Teixeira, 2018; Wu *et al*., 2020).

4.6. Impact of biofilms on VVC pathogenesis and treatment

4.6.1. Immune evasion and persistence in biofilm-associated VVC

Research revealed that biofilms facilitate immune evasion by *Candida* cells, allowing them to persist and establish chronic infections. The biofilm matrix and the persister cells within the biofilms contribute to the reduced recognition and clearance by the host immune system. Moreover, biofilms can modulate the host immune responses and impair the immune cell functions, leading to an ineffective immune defence against *Candida* spp. (Rodríguez-Cerdeira *et al*., 2020).

4.6.2. Strategies for targeting and disrupting *Candida* biofilms

A recent study conducted by Ramage *et al*., (2023) highlighted that developing effective strategies to target and disrupt *Candida* biofilms is crucial for improving VVC treatment outcomes. These approaches include biofilm-disrupting agents, combination therapies, and the development of novel antifungal agents that are specifically designed to target the biofilm-associated *Candida* cells (Fig. 1). Active research areas are necessary to understand the molecular mechanisms underlying biofilm formation and identifying the critical targets for intervention.

5. Diagnostic work-up for vulvovaginal Candidiasis

Improved diagnostic techniques have also emerged, allowing for more accurate and rapid identification of *Candida* spp., in addition to the assessment of vaginal microbiota composition (Neal and Martens, 2022). These diagnostic advancements can potentially enhance the early detection and management of VVC.

5.1. Microscopic examination and culture-based methods

Microscopic examination of the vaginal samples allows for direct visualization of the *Candida* cells. Detection of budding yeast cells and pseudohyphae in wet mounts or Gram-stained smears provides preliminary evidence for VVC. Additionally, the culture-based methods involve isolating and identifying *Candida* spp. from the vaginal swabs or samples using selective media. However, these methods have limitations regarding sensitivity, specificity, and turnaround time (Arya and Rafiq, 2023).

5.2. Molecular diagnostics for identification of *Candida* spp.

A previous study reported by Magalhães *et al*., (2022) revealed that molecular techniques, such as polymerase chain reaction (PCR), have emerged as valuable tools for the rapid and accurate identification of *Candida* spp. The PCR-based assays target the specific *Candida* genes or regions, allowing for species-specific detection and differentiation. These methods offer improved sensitivity and specificity compared to the traditional culture-based techniques.

5.3. Advancements in the laboratory techniques

5.3.1. Next-generation sequencing for studying the vaginal microbiota

Reports suggest that the next-generation sequencing (NGS) technologies have revolutionized the study of microbial communities, including the vaginal microbiota. NGS allows for comprehensive profiling of the microbial populations, enabling the identification of *Candida* spp. and the assessment of their relative abundances in the vaginal environment (Ceccarani *et al*., 2019). This approach provides valuable insights into the complex dynamics of the vaginal microbiota in VVC.

5.3.2. Proteomic and metabolomic approaches for biomarkers discovery

The proteomic and metabolomic techniques have shown promise in identifying the potential biomarkers for VVC. These approaches involve comprehensively analysing the proteins or metabolites in the samples and/ or vaginal secretions. By comparing the profiles of VVC patients with the healthy individuals, specific biomarkers associated with VVC can be identified. These biomarkers may aid in early diagnosis, monitoring treatment response, and predicting the disease outcomes (Schumacher-Schuh *et al*., 2022).

5.4. Point-of-care diagnostics and prospects

5.4.1. Rapid and sensitive tests for VVC diagnosis

According to several previous studies, efforts are underway to develop rapid and sensitive point-of-care diagnostic tests for VVC (Brown and Drexler, 2020; Arafa *et al*., 2023). These tests aim to provide quick and accurate results at the point of patient care, thus eliminating the need for laboratory processing. Several diagnostic technologies, such as immune-chromatographic assays and nucleic acid amplification tests, are being explored for their potentials to detect *Candida* infections with high sensitivity and specificity.

5.4.2. Advances in biosensor and nanotechnology-based diagnostics

Biosensors and nanotechnology-based diagnostics hold promise for the future of VVC diagnosis. These approaches utilize nanomaterials, such as nanoparticles or nanowires, which are integrated with specific biomolecular recognition elements, to detect *Candida* cells or the biomarkers associated with VVC. These biosensors offer several advantages, such as rapid detection, high sensitivity, and the potential for miniaturization, enabling portable and friendly use of the diagnostic devices. As the research for diagnostic techniques has advanced, developing novel and more accurate diagnostic methods for VVC holds excellent potential (Hussain *et al*., 2020). These advancements will contribute to early detection, effective management, and improved outcomes for individuals with VVC.

6. Treatment strategies, challenges, and management of recurrent vulvovaginal Candidiasis

6.1. Antifungal agents and their efficacy

Azoles such as fluconazole are the most commonly used antifungal agents for VVC treatment. They inhibit the synthesis of ergosterol, a vital component of the fungal cell membranes. Polyenes, such as nystatin, bind to the ergosterol and cause cell membrane damage. Echinocandins, like caspofungin, target the fungal cell wall synthesis. These antifungals exhibit varying efficacies against *Candida* spp., with azoles generally being the first line of treatment (Phillips *et al*., 2022).

6.2. Antifungal resistance and emerging challenges

Several studies reported that emergence of the antifungal resistance poses challenges in VVC treatment. *Candida* spp. can develop more than one resistance mechanism, such as alterations in the drug targets and efflux of the pump overexpression. This resistance limits the effectiveness of the antifungal therapy. Therefore, surveillance of the antifungal resistance and development of new treatment strategies

are essential for managing VVC (Yassin *et al*., 2020; Arastehfar *et al*., 2021).

6.3. Recurrence (RVVC) prevention strategies

Recurrent vulvovaginal Candidiasis (RVVC) represents four or more episodes of VVC within a year. The management strategies for RVVC include long-term or intermittent prophylactic antifungal therapy, maintenance therapy, and identifying and modifying the underlying risk factors, such as uncontrolled diabetes and/ or immunosuppression. Lifestyle modifications, including avoiding irritants and practicing good hygiene, may also be highly recommended (Rosati *et al*., 2020; Donders *et al*., 2022).

6.4. Alternative and combination therapies for RVVC

In cases of RVVC that are refractory to the standard antifungal therapy, alternative treatment options can be considered. These may include a combination of the antifungal regimens, such as using azoles with topical antifungals or boric acid suppositories. The immunomodulatory agents, like the interferon-gamma, have also shown promise in reducing RVVC recurrence rates (Felix *et al*., 2019). Probiotics, particularly the Lactobacilli, have been investigated for their potentials in preventing and treating VVC. These beneficial bacteria can restore the balance of the vaginal microbiota, inhibit *Candida* growth, and modulate the immune response. The probiotics can be administered orally or vaginally and may be used alone or in combination with the antifungal therapy (Shenoy and Gottlieb, 2019). Furthermore, several herbal and natural products have displayed antifungal potential against *Candida* spp. For example, the pea protein, grape seed extract, and lactic acid oil, have expressed inhibitory effects against *Candida* growth. However, further research is needed to determine their efficacies, safety, and optimal dosage regimens for VVC treatment (Alam and Khan, 2021; Paterniti *et al*., 2022).

Conclusion

Effective management of VVC involves appropriate antifungal agents, addressing antifungal resistance, tailored approaches for RVVC, and exploring alternative and complementary therapies. Continued research and clinical trials are essential for optimizing the treatment strategies and improving the outcomes for those individuals with VVC. Recent advances in vulvovaginal Candidiasis research have provided valuable insights into the molecular mechanisms driving its pathogenesis. The researchers and clinicians can develop more targeted and effective preventive strategies, therapeutic interventions, and diagnostic approaches through unraveling these mechanisms. Continued research in this field holds promise for improving the management and outcomes of the vulvovaginal Candidiasis, ultimately benefiting the women's health and well-being.

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Conflicts of interests

The authors declare they do not have any conflicts of interest.

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Author's Contributions

All authors contributed equally in preparing this manuscript.

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