GYNECOLOGY

Recurrent vulvovaginal candidiasis

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Recurrent vulvovaginal candidiasis (RVVC) is a common cause of significant morbidity in women in all strata of society affecting millions of women worldwide. Previously, RVVC occurrence was limited by onset of menopause but the widespread use of hormone replacement therapy has extended the at-risk period. *Candida albicans* remains the dominant species responsible for RVVC, however optimal management of RVVC requires species determination and effective treatment measures are best if species-specific. Considerable progress has been made in understanding risk factors that determine susceptibility to RVVC, particularly genetic factors, as well as new insights into normal vaginal defense immune mechanisms and their aberrations in RVVC. While effective control of RVVC is achievable with the use of fluconazole maintenance suppressive therapy, cure of RVVC remains elusive especially in this era of fluconazole drug resistance. Vaccine development remains a critical challenge and need.

Key words: antifungals, antimycotics, *Candida* vaginitis, vaginal candidosis, vulvovaginal candidiasis

Originally termed "acute *Candida* vaginitis," vaginal infection by *Candida* species has transformed into the concept of vaginal candidiasis or candidosis in the United Kingdom, due to recognition of a wider spectrum of symptomatic and asymptomatic disease.[1] Subsequent recognition that the dominant site of inflammation and source of symptoms is the vulva led to the term "vulvovaginal candidiasis" (VVC). While most episodes of symptomatic disease appear as sporadic attacks of acute VVC, some women have more chronic or long-term daily manifestations and symptoms are infrequently diagnosed as mycotic in origin.[2] Yet another subgroup has emerged with recurrent episodes, being entirely asymptomatic between episodes (recurrent VVC [RVVC]). The entity of RVVC has been defined as at least 3 symptomatic episodes in the previous 12 months, although some investigators demand yet an additional episode, ie, 4 attacks.[3,4] This is an entirely arbitrary differentiation, not based on any data or study and likely women so identified by each definition are identical.

It has become impossible in any open, free society to perform epidemiologic studies and determine the frequency of women with RVVC.[4,5] This is, firstly, a consequence of the widespread availability of over-the-counter (OTC) antifungal agents. Procurement of the easily available, numerous highly effective topical antimycotic agents, although controversial, can be considered a boon to women's health. OTC availability clearly has given women access to rapid symptom relief, but is still not inexpensive and open access should have been accompanied by a diagnostic test that would have allowed a woman to correctly diagnose yeast as the cause of her symptoms. Regrettably self-diagnosis is unreliable, with significant overdiagnosis of VVC in the presence of extremely nonspecific and common symptoms. Numerous studies have shown the drawbacks of OTC availability of antifungal agents.[6] Fortunately, the excessive use and overuse of such topical agents has had infrequent adverse consequences, safety has been maintained, and drug resistance as a consequence of frequent use remains rare.

The inadequacies of self-diagnosis of VVC are compounded by practitioner overdiagnosis and underdiagnosis, with US standards comparable to those of syndromic methods in nonindustrialized countries. Current clinical approaches are too often based on empiricism and trial and error. These factors have contributed to poor data availability of the frequency of both acute VVC and RVVC.[5] Estimation of the prevalence of RVVC is similarly marred by physician diagnostic inaccuracies. A recent study using online computer technology reaffirmed a large earlier study reporting self-professed RVVC in 6-9% of women.[7,8]

Of note, in an expanding population of postmenopausal women isolated studies have supported the clinical impression that a growing number of older women remain at risk of VVC and RVVC as the result of hormone replacement therapy, especially vaginal topical use.[9] It is estimated that RVVC affects approximately 138 million women worldwide annually and 492 million over their lifetimes (David Denning, MD oral communication July 24, 2015). Unfortunately true population-based studies of RVVC are rare. Moreover, the natural history of RVVC over a lifetime has not been addressed. Foxman et al[8] obtained data on duration of symptoms linked with age in 247 women. Most women reported duration of RVVC to be 1-2 years although a substantial number had symptoms for 4 or 5 years and some very much longer, with risk and symptoms lasting decades.

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Given that *C albicans* remains responsible for >90% of episodes of

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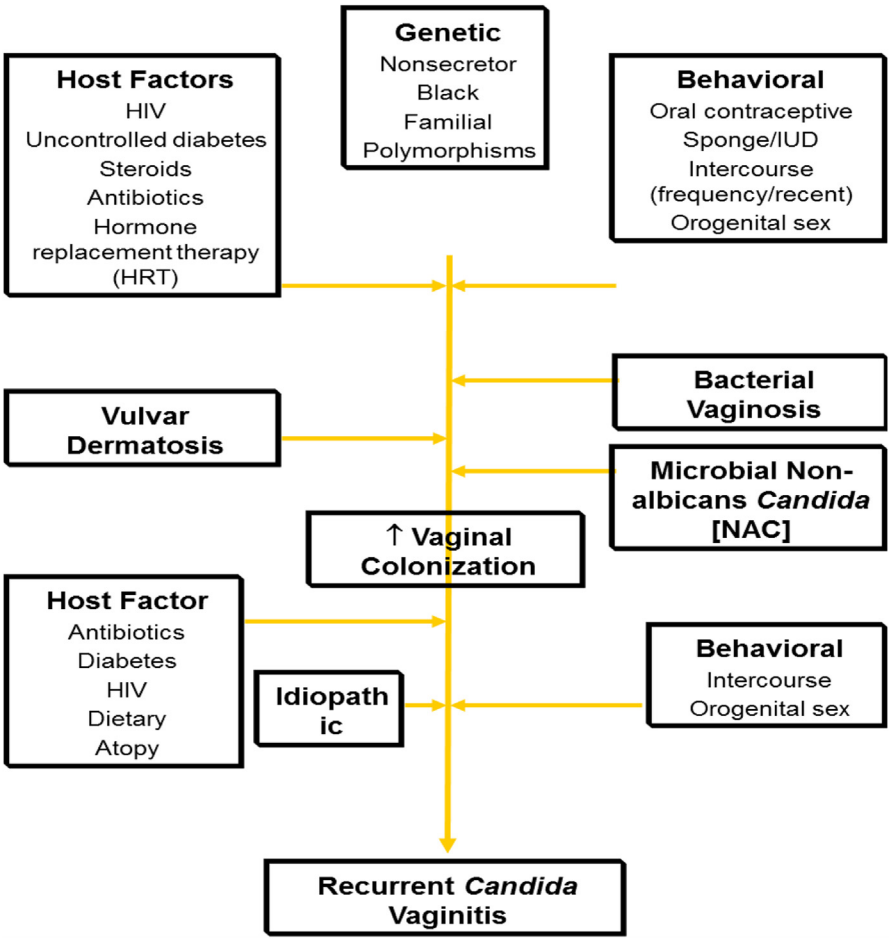
FIGURE
Pathogenesis of recurrent vulvovaginal candidiasis



IUD, intrauterine device; *RVVC*, recurrent vulvovaginal candidiasis.

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acute sporadic VVC in most studies worldwide, it is not surprising that *C albicans* similarly is responsible for the majority of infections in women with RVVC.[4,10-13] Approximately 85-95% of women with RVVC have azole-sensitive *C albicans* as the causative pathogen, implying that the host rather than the pathogen contributes dominantly to the pathophysiology of RVVC.[4,10] Of the non-*albicans Candida* species, *C glabrata* is the most frequently isolated species from the vagina in symptomatic and asymptomatic women.[4] Risk factors for *C glabrata* include type 2 diabetes, postmenopausal status, and older age.[4] The recent introduction of glycosuria-inducing agents to treat type 2 diabetics is also reported to increased prevalence VVC due to *C glabrata*.[14] In contrast to adults with invasive candidiasis and candidemia, azole exposure has not emerged as a risk factor for *C glabrata* in women with RVVC. It would appear that all non-*albicans Candida* species have substantially reduced capacity to express virulence characteristics and hence serve as vaginal pathogens. The implications are important in that the mere isolation of *C glabrata* and other non-*albicans* species in symptomatic women with vaginitis does not confirm causality. A cause-effect likelihood is far lower than that defined for *C albicans*, with likelihood of *C glabrata*, isolated from the vagina, being responsible for symptoms no higher that 20-30%.[15] Accordingly, in such women other causes for symptoms require active exclusion, before embarking on antifungal therapy, which is less likely to eradicate these low virulence, innocent bystanders also more resistant to antifungal agents.[16] Occasionally major geographic differences in *Candida* species distribution are reported and more reports usually indicate a higher frequency of *C glabrata* occurrence.[10]

Pathogenesis of RVVC

Candida blastospores (yeast) migrate from the lower gastrointestinal tract to the adjacent vestibule and vagina. This is a similar route taken by vaginal *Lactobacillus* species. Colonization of the vagina follows usually in low numbers after adherence of *Candida* to vaginal epithelial cells. Colonization resistance is poorly studied and understood but colonization is enhanced by an estrogen-influenced environment following menarche and declines in the postmenopause period. In healthy women not prone to RVVC, asymptomatic colonization may persist for months and years as yeasts live in symbiosis with vaginal microbiota. Acute symptomatic VVC follows a breakdown in this relationship and entails either a triggered overgrowth of *Candida* organisms or alteration in the host protective defense mechanisms, which act to maintain low numbers of yeast organisms and at the same time deliberately down-regulate the mucosal immune inflammatory response aimed at tolerating the presence of low numbers of yeast. An increased rate of vaginal colonization represents but 1 phase of susceptibility to RVVC and causes may be genetic, biologic, or behavioral as shown in the Figure. Description of *Candida* virulence factors is outside the scope of this review.

The innate immune system provides the first barrier against vulvovaginal *Candida* infections. Pattern recognition receptors on innate immune cells sense molecular moieties on the surface of yeast, and thereafter induce an intracellular signal within epithelial cells that stimulates production of effector molecules such as proinflammatory cytokines