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FEMALE GENITAL TRACT INFECTIONS (J SOBEL, SECTION EDITOR)

Vulvovaginitis Caused by *Candida* Species Following Antibiotic Exposure

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Abstract

Purpose of Review Goal was to review epidemiology, pathophysiology, and prevention of post-antibiotic *Candida* vulvovaginitis (VVC).

Recent Findings Antibacterial therapy, whether systemic or locally applied to the vagina, represents the single most frequent and predictable cause or triggering mechanism of symptomatic vulvovaginal candidiasis (VVC). Such initiating mechanisms may precipitate sporadic or recurrent episodes of VVC. In spite of this widely recognized association, the exact mechanism whereby antibiotics of all classes cause acute exacerbation of symptomatic vaginal disease remains largely unstudied and therefore largely unknown. Pathophysiology is hypothesized to be reduction or alteration of vaginal microbiome restraints of yeast colonization, proliferation, and expression of virulence characteristics.

Summary The predictable link between antibiotic use and post-antibiotic VVC affords practitioners an opportunity for timely intervention using selective, convenient antimycotics usually drugs but possibly probiotic measures. Indications and limitation of these steps are discussed.

Keywords Vulvovaginitis · Antibiotics · Candidiasis · *Candida* species

Introduction

Both sporadic and recurrent vulvovaginal candidiasis (RVVC) infections occur worldwide affecting all strata of society [1]. As such, the international burden of this common infection is enormous both in terms of human suffering as well as economic consequences [2]. The high prevalence of this common infection continues in spite of the availability of a wide array of antifungal drugs both oral and topical [1]. Among the most common and widely recognized triggers or precipitating factors for individual episodes of VVC is exposure to antibacterial agents, whether exposure follows systemic or local antibiotic administration [1]. Little progress has been made in preventing antibiotic-induced VVC and if anything the incidence of this complex infection is on the increase due to widespread increased abuse of antibiotics. Unfortunately, even less progress has been forthcoming in understanding the pathophysiology of VVC following antibiotic administration. Yet another consequence of the widespread increased use of antibiotics and associated VVC is the growing problem of antifungal drug resistance [3]. In the current review, we focus on the epidemiology, pathogenesis, and prevention of antibiotic-induced VVC with particular reference to RVVC.

This article is part of the Topical Collection on *Female Genital Tract Infections*

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Epidemiology

There are no accurate numbers indicating the exact frequency or risk of post-antibiotic VVC, although estimates suggest a global risk of 10–30% (Table 1). Unfortunately, numbers depend upon reliability of methods used to confirm the diagnosis of VVC. Moreover, access to over-the-counter (OTC) medications allows and encourages women to self-diagnose vulvovaginal symptoms. All too often reports of post-

Table 1 Frequency estimates of post-antibiotic VVC

Reference	Year	No. of patients evaluated	Culture confirmation	Antibiotics	Colonization or VVC episodes	Risk of VVC
Caruso [7]	1964	59	Yes	Tetracycline vs tetracycline + amphotericin B	Increase from 7 to 24%	2.36 [95% CI 1.21–4.59]
Oriel and Waterworth [8]	1975	204	Yes	Tetracycline vs minocycline	Increase from 13 to 29%	2.21 [95% CI 1.38–3.51]
Iravani and Richard [14]	1986	102	Yes	Amoxicillin–clavulanic acid Cefaclor	16% 13%	1.6 [95% CI 0.99–2.6]
Bluestein et al. [12]	1991	74	Yes	Multiple	32% (24/74)	2.15 [95% CI 1.54–3.01]
Mac Donald et al. [10]	1993	4445	No	Multiple		2.3 [95% CI 1.9–3]
Geiger et al. [18]	1996	Case: 64 Control: 431	Yes	Multiple	11%	0.81 [95% CI 0.34–1.87]
Glover and Larsen [17]	1998	250	Yes	Penicillin, macrolides, nitrofurantoin, cephalosporins, metronidazole, sulfonamides	6%	0.43 [95% CI 0.19–0.98]
Spinillo et al. [11]	1999	Cases: 684 Controls: 90	Yes	Penicillin, cephalosporins, quinolones, trimethoprim-sulfamethoxazole, others	55%	1.75 [95% C1 1.33–2.32]
Menday [19]	2002	1152 (randomized double blind trial: 4 arms)	No	Pivmecillinam tds-7	13%	2.2 [95% CI 0.8–5.6]
				Pivmecillinam bid-7	7%	1.1 [95% CI 0.4–3.4]
				Pivmecillinam bid-3	6%	1 [95% CI 0.3–3.1]
Glover and Larsen [17]	2003	316	No	Ceftriaxone metronidazole, trimethoprim—sulfamethoxazole, amoxicillin, doxycycline	1.2% (within 1 month of antibiotic use)	–
Pirotta et al. [13]	2003	1042	No	Unspecified	23%	0.9
Pirotta et al. [20]	2004	235	Yes	Unspecified (with oral or vaginal *Lactobacillus*)	23%	1.06 (oral *Lactobacillus*) [95% CI 0.58–1.94] 1.38 (vaginal *Lactobacillus*) [95% CI 0.75–2.54]
Pirotta et al. [21]	2006	257	Yes	Unspecified	Increase from 21% to 37%	1.46
Tabrizi et al. [4]	2006	90	Yes (culture vs PCR)	Variety (non-genital infections)	Culture: 8.8% (8/90) PCR: 13.3% (12/90)	–
Xu et al. [15]	2008	80	Yes	Unspecified	Colonization: 37% Symptomatic VVC: 22.2%	3.33 [95% CI 1.03–10.79]

antibiotic VVC is based upon self-reported symptoms without culture confirmation.

Other variables indicate type and duration of antibiotic therapy, as well as existence of concurrent and coexistent risk factors, e.g., topical steroids, estrogen therapy, and vulvar disease such as lichen sclerosus (Table 2). Hence multiple factors determine risk of VVC following antibiotics. Numbers should be based upon *Candida* culture positive diagnosis and not on signs and symptoms alone. Although use of PCR-based methods indicates an even higher frequency of *Candida* detection than the culture method, most of these patients are asymptomatic with extremely low *Candida* microbial load [4]. Another variable in defining risk of VVC depends upon whether antibiotics are prescribed for coexistent vaginal infections (e.g., bacterial vaginosis) or alternatively for extragenital infections. Woods et al. in 1951 first reported VVC complicating antibiotic therapy and this observation was rapidly confirmed by Miller [5, 6].

Caruso first reported that tetracyclines were associated with an increase in the percent of women colonized by yeast [7]. Similar results were reported by Oriel and Waterworth, once more with tetracycline but this time noting increased VVC episodes, colonization increased from 13 to 29% [8]. Confirmation by Waterworth was soon forthcoming [9].

Cohort and case-control studies have found a significant association between antibiotics and developing VVC [10, 11]. In a community-based study, Bluestein observed that 28% of 78 women developed symptomatic microbiologically proven VVC following antibiotic exposure [12].

Table 2 Factors determining risk of post-antibiotic VVC

- Host factors
  - Genetic susceptibility
  - Past H/0 RVVC
  - Past H/0 antibiotic-induced VVC
  - Coexistent host disease
  - Vulvar disease (L. sclerosus)
  - Bacterial vaginosis
  - Coexistent host factors
  - Steroids
  - Estrogen therapy, (topical, systemic)
  - Vaginal microbiome
  - Existent vaginal *Candida* colonization
- Drug factors
  - Duration of therapy
  - Route of infection—local vs systemic
  - Antibiotic characteristics—broad spectrum
- Mycotic factors
  - -? *Candida* species/strains

Spinillo et al. in a large case-control study of 684 women with symptomatic VVC determined the risk of developing symptomatic VVC to be 1.75 (C.I. 1.33–2.32) compared to 901 control subjects without VVC [11]. The prevalence of exposure to antibiotics among patients with repeated vaginitis was 2.3%, with risk of VVC attributable to antibiotic exposure of 12.8%. This study more than any other confirmed that antibiotic therapy is a short-term risk factor for VVC.

In a study using vaginal antifungal prescriptions as a surrogate measure of VVC, MacDonald et al. reported a relative risk of (2.3) of VVC after taking antibiotics, with risk highest in those 30–46 years (RR 6.0). The attributable risk was the highest among those taking cephalosporins (AR 12.8%) [10]. In a case-control study comparing previous antibiotic exposure among women using vaginal antifungal agents and matched controls, antibiotic exposure during the previous 28 days was significantly higher among those using antimycotics with an odds ratio of 5.5 (95% C.I. 3.8–7.9) [10].

In an Australian study, 23% of women who had taken antibiotics within the previous month experienced symptoms of vulvovaginitis although VVC was not confirmed by culture [13].

All classes of oral and topical antibiotics have been associated with post-exposure VVC and no class appears exempt from this complication, although not all antibiotics appear to have the same risk. Duration of therapy also appears critical with single day and short course therapy less likely to result in VVC. Topical vaginal antibacterial therapy is especially likely to cause VVC and appears most frequent with topical clindamycin. In general, systemic broad spectrum antibiotics such as tetracyclines often prescribed for long-term acne use have also been identified as frequent triggering agents. On the other hand, vaginal metronidazole prescribed frequently for bacterial vaginosis, with spectrum of activity linked to anaerobic microorganisms and largely sparing *Lactobacillus* species, is only too often associated with secondary post-metronidazole VVC, although the role of the BV-associated dysbiosis in contributing to this frequent complication is unknown.

Iravani and Richard reported symptomatic *Candida* vaginitis in 16% and 13% of women receiving amoxicillin–clavulanic acid and cefaclor treatment for urinary tract infections [14]. Xu et al. reported that 22% of women receiving short-term antibiotics developed culture positive VVC following antibiotics, although in contrast to most investigators, baseline vaginal yeast cultures did not predict subsequent VVC [15].

Not all investigators have reported an association between antibiotic exposure and VVC (Glover and Larsen). In a study of antifungal drug use for VVC, in a rural population of non-pregnant women, no association of antibiotic use as a putative cause of VVC was found [16, 17]. This negative study was not however based upon VVC signs, symptoms, and culture

confirmation and may also reflect overall pharmaceutical use in a unique population. A similar negative association was reported in a case-control study [18].

Pathogenesis (Table 2)

Both vaginal and intestinal yeast colonization increases significantly following systemic antibiotic administration with vaginal yeast colonization increased after vaginal-only topical antibiotic exposure and the dominant species being *C. albicans* [8, 15, 21, 22]. Baseline vaginal colonization with *Candida* species is significantly associated with post-antibiotic symptomatic VVC, with vaginal colonization generally found in 10–25% of healthy women [21]. Self-assessed proneness to VVC after antibiotic exposure also predicts likelihood of VVC under these circumstances [21].

Extremely limited data suggest paradoxically that antibiotics may inhibit yeast growth in vitro and can be dismissed, but there is also little evidence of enhanced *Candida* virulence directly due to antibiotic exposure in vitro [8, 23, 24]. Investigations more than 5 decades ago concluded that the single factor in the vaginal overgrowth of *C. albicans* following the use of antibiotics was the elimination of bacteria competing with this fungus for environmental food supply [5]. This concept of a direct effect of antibiotics depleting or reducing protective vaginal bacterial species in facilitating yeast overgrowth has dominated pathophysiology-linked hypotheses of causation of post-antibiotic VVC. Not surprisingly, theories have focused on so called "healthy" protective dominant species viz. *Lactobacillus* species [25].

Such protective lactobacilli have been thought to control vaginal microbiota including overgrowth of vaginal *Candida* spp. by reducing epithelial cell adherence which facilitates in vivo persistence, as well as elaboration of protective chemicals, molecules, and other moieties such as lactic acid, hydrogen peroxide, and bacteriocins. However, critical to this much-quoted dogma is lack of data confirming a critical reduction of number or function of protective lactobacilli or other bacterial species following antibiotics. This is in spite of the plethora of publication using quantitative and qualitative molecular technologies including next generation sequencing to evaluate vaginal microbiota but which lack of focus of the specific effects of antibiotics or the vaginal microbiome. Previously all investigations of vaginal microbiota were limited to culture-based studies, entirely missing the many vaginal bacterial species potentially critical to understanding pathogenesis of VVC. It was widely assumed that antibiotic-induced VVC was the consequence of reduction of protective *Lactobacillus* species but studies lacked ability to accurately perform quantitative cultures. This applies both to sporadic or recurrent VVC, whether or not related to antibiotic exposure. Non-quantitative studies performed in the past were unlikely to be of any value in determining the protective role of *Lactobacillus* spp.

Moreover, even suspected protective *Lactobacillus* spp. such as *L. crispatus* may vary considerably in individual strain capacity to inhibit yeast proliferation or growth. The lack of data of any kind confirming the critical role of lactobacilli in VVC has not prevented an avalanche of therapeutic attempts and manuscripts evaluating probiotic therapy to prevent VVC. Similarly, lack or loss of vaginal lactobacilli has not been documented in women taking antibiotics [26–28].

Most importantly, VVC is not more frequent in women lacking lactobacilli [28]. In addition, there is no evidence that women with idiopathic recurrent VVC, likely of poly-genetic underlying basis, have a vaginal microbiota deficient in lactobacilli [26–27]. Nevertheless, the eradication or reduction of certain bacterial species or strains, aerobes or anaerobes, may well free *Candida* organisms colonizing asymptomatic women, from replicative restraint or virulence control mechanisms.

The microbial protective mechanisms responsible for maintaining a healthy, tolerant equilibrium between vaginal microbiota and *Candida* microorganisms in women with asymptomatic colonization appear to await imminently doable quantitative, qualitative, and functional studies involving next generation sequencing as well as further evaluation of the vaginal metabolome. It is also apparent that explanations for bacterial microbiome and mycobiome interaction to date have ignored several concepts. (i) The possibility that antibiotics without reducing bacterial (e.g., lactobacilli) numbers to a measureable extent, nevertheless damage the microbiome resulting in elaboration of molecules, e.g., heat shock protein (HSP) that could enhance yeast overgrowth and virulence expression. (ii) Also not considered is the role of the vaginal epithelial cells as a source of cytokines that might be elaborated in response to antibiotics that directly impact upon yeast proliferation and invasive capacity. Relatively few studies have been completed on how the vaginal microbiome affects host gene expression in vaginal epithelial cells [29, 30]. Thus antibiotic-induced microbiome changes could rapidly influence epithelial cell elaboration of cytokines impacting yeast overgrowth or virulence. Recent studies have further emphasized the role of virulent *Candida* invading vaginal epithelial cells as an essential part of VVC [31].

Once more, it should be emphasized that the majority of women taking antibiotics by any route, do not develop symptomatic acute VVC although many do show increased colonization rates. So why are some women protected from this complication? Clearly, a part explanation once more relates to pre-antibiotic vaginal colonization as a prerequisite, perhaps even status of intestinal colonization. However, overgrowth and replication restrictions may exist in the form of innate and adaptive immune "brakes" that prevent onset of acute inflammation. Our ignorance of the pathophysiology

of VVC currently limits our understanding of pathophysiology of antibiotic-induced VVC.

Clinical Aspects of Antibiotic-Induced VVC

There appears to be nothing unique in the clinical picture of VVC following or accompanying antibiotic use. Symptoms appear within a variable time during or following cessation of antibiotic use. Microbiologic studies indicate *C. albicans* as the most prevalent pathogen. Similarly, treatment with antimycotics follows basic therapeutic principles.

Prevention of Antibiotic-Induced VVC

There are no established guidelines that specifically relate to prevention of VVC following exposure to antibiotics regardless of route of administration. Moreover, most clinicians are insensitive to this frequent complication and have traditionally chosen to wait for the inevitable attack to present itself. In general, women for whom antibiotics are prescribed when mentioning this possibility to the prescribing practitioner are usually ignored.

The most widely prescribed convenient and putatively effective prevention measure is use of oral fluconazole 150 mg prescribed together with antibiotics. The optimal dose and frequency of prophylactic fluconazole is unknown and has not been evaluated in a randomized controlled trial. In the Wayne State University Vaginitis clinic, the prophylactic regimen currently used consists of fluconazole 150 mg given at the beginning and end of antibiotics or once weekly as long as the antimicrobial are taken. Clinical experience in the absence of a controlled study suggests high efficacy. Less convenient single dose topical azole antimycotics could also be used. Given the frequency of post-antibiotic VVC, some manufactures currently provide combination therapy of antibacterial and antimycotic creams or suppositories usually miconazole to prevent consecutive VVC following vaginal treatment for bacterial vaginosis.

Another option is prescription of simultaneous oral or vaginal probiotics usually consisting of *Lactobacillus* preparations; based upon the premise that women with VVC have ineffective or reduced vaginal or intestinal *Lactobacillus* numbers, or that these criteria are likely to develop during antibiotic therapy. This represents a leap of faith or extrapolation based upon zero data and proof of efficacy. In a large prospective placebo-controlled study of women receiving short-term oral antibiotics for non-gynecologic infections, neither oral nor vaginal *Lactobacillus* probiotics were effective in preventing post-antibiotic VVC [16]. It is likely that many similar studies will follow.

Conclusion

Although antimicrobial use emerges as the most common precipitating factor in causing acute symptomatic VVC; the pathogenesis of this common complication of antibiotics remains unknown. The availability of next generation sequencing and molecular methods to accurately define vaginal microbiota has not yielded any additional data in explaining causation of post-antibiotic VVC. In addition, no clinical studies have been performed to optimize prevention of this extremely common complication of widespread antibiotic use. Based upon clinical experience, antimycotic prophylaxis appears effective and is recommended; however, additional study confirmation is needed.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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