Curr Infect Dis Rep (2013) 15:104–108
DOI 10.1007/s11908-013-0325-5

HOT TOPIC

Mixed Vaginitis—More Than Coinfection and With Therapeutic Implications

Jack D. Sobel · Chitra Subramanian · Betsy Foxman · Marilyn Fairfax · Scott E. Gygax

Published online: 27 January 2013

Abstract Mixed vaginitis is due to the simultaneous presence of at least two vaginal pathogens, both contributing to an abnormal vaginal milieu and, hence, symptoms and signs of vaginitis. In mixed vaginitis, both pathogens require specific therapy for complete eradication of concurrent manifestations. In coinfection, although two pathogens are identified, a potential pathogen may be present but may not be a cause of existing vaginal symptoms. Although data remain sparse, mixed vaginitis occurs rarely (<5 %). By contrast, pathogen coinfection occurs frequently in women with vaginitis. Approximately 20 %–30 % of women with bacterial vaginosis (BV) are coinfected with *Candida* species. Coexistence of BV pathogens and *T. vaginalis* is even more common, with coinfection rates of 60 %–80 %. Both coinfection and mixed vaginitis have significant clinical and therapeutic implications and are worthy of further investigation.

J. D. Sobel · C. Subramanian
Division of Infectious Diseases,
Wayne State University School of Medicine, Detroit, MI, USA

B. Foxman
School of Public Health, University of Michigan,
Ann Arbor, MI, USA

M. Fairfax
Department of Pathology,
Wayne State University School of Medicine, Detroit, MI, USA

S. E. Gygax
Femeris Women's Health Research Center, Medical Diagnostic Laboratories, A Member of Genesis Biotechnology Group,
Hamilton, NJ, USA

J. D. Sobel (✉)
Division of Infectious Diseases, Harper University Hospital,
3990 John R,
Detroit, MI 48201, USA
e-mail: Jsobel@med.wayne.edu

Keywords Vaginitis · Candida · Bacterial vaginosis · Trichomoniasis · Coinfection · Mixed infection

Introduction

In contrast to other anatomical sites, the number of pathogens causing vulvovaginal symptoms or vaginitis is small (Table 1) [1, 2]. Nevertheless, establishing the etiology of vulvovaginal infection is not simple [3–7]. Simply identifying *in situ* the presence of a known pathogen does not establish a cause–effect relationship with clinical presentation. The purpose of this review is to describe the epidemiology of vaginitis in the presence of two or more potential vaginal pathogens, review pathogenic considerations, and discuss the therapeutic implications thereof. In this review, we first distinguish mixed vaginitis from vaginal coinfections.

The concept of mixed vaginitis has escaped clinical scrutiny and definition. How does one even define mixed vaginitis? In its simplest form, mixed vaginitis refers to the simultaneous presence of two or more potential pathogens in the lower genital tract, regardless of the clinical significance of the individual pathogens. Accordingly, given the frequent occurrence of *Candida* vaginal colonization, this definition would likely result in the highest estimate of mixed vaginitis prevalence. Finding a positive yeast/*Candida* species culture in the presence of vaginal trichomoniasis or bacterial vaginosis (BV) may constitute a mixed vaginal infection but not mixed vaginitis, since positive vaginal cultures may reflect only *Candida* spp. colonization, a common finding in 10 %–15 % of healthy reproductive age women. On the other hand, if the definition of mixed vaginitis excluded patients with vaginal yeast colonization defined by a positive vaginal culture, epidemiologic estimates would shift considerably and would include far fewer cases. Mixed vaginitis must be differentiated from the more common scenario of vaginal coinfection with two or more potential vaginal pathogens (Table 2).

Table 1 Potential concomitant vaginal pathogens

1.	Trichomonas vaginalis
2.	Chlamydia trachomatis (cervicitis not vaginitis)
3.	Neisseria gonorrhoeae (cervicitis not vaginitis)
4.	Bacterial vaginosis (BV) associated microorganism (BVAB)
5.	Herpes simplex (cervicitis not vaginitis)
6.	*Candida* species
7.	Streptococcus pyogenes (Group A streptococcus)

Mixed vaginitis implies that at least two or more pathogenic processes, rather than two pathogens per se, coexist in the vagina, each contributing to symptoms and signs [8]. The contemporaneous process may be independent or dependent (Table 3). By contrast, if only one pathogen is responsible for symptoms, the other can be ignored, as is the case in coinfection. In attempting to reach an acceptable definition of mixed infection, one of necessity must retain a reasonable link to therapeutic implications. For example, *Candida* is unlikely to contribute to the typical symptoms of malodorous vaginal discharge. Therefore, a laboratory report of positive *Candida* culture in women with malodorous discharge caused by BV or trichomoniasis would not mandate a need to add antifungal chemotherapy, except under exceptional circumstances. On the other hand, finding a positive culture or PCR result for Chlamydia or *Neisseria gonorrhoeae* in a patient with BV unquestionably requires therapy of all pathogens so identified, regardless of contribution to symptomatology, because the presence of Chlamydia or *N. gonorrhoeae* is significant in the absence of symptoms [9].

Definitions of mixed vaginitis are contained in Table 2, and clearly, definitions 1 and 2 are not mutually exclusive. *Candida* organisms are most frequently present as colonizing microorganisms not contributing to the clinical symptoms but can be an active participant adding to clinical inflammation, especially of the vulva (vulvitis), as well as altering discharge characteristics and adding pruritus to the symptom complex. In the latter scenario of true mixed vaginitis with *Candida* spp. participating, not only are *Candida* cultures positive, but also signs of candidiasis are evident and the 10 % KOH microscopy examination may also be positive. Positive microscopy indicating the high titer presence of *Candida* and hyphal formation are infrequently observed with colonization only. In contrast to the typical scenario of *Candida* vaginitis (VVC) with normal vaginal pH, mixed vaginitis is invariably characterized by elevated pH (>4.5).

Table 2 Definition of mixed vaginitis

1.	Concomitant presence of ≥2 vaginal pathogens, regardless of presence or contribution to symptoms or need for therapy (coinfection).
2.	Presence of ≥2 vaginal pathogens, but excluding women found to be colonized with *Candida* species, the latter not contributing to the clinical syndrome and, hence, not justifying additional antimycotic therapy.
3.	Concomitant presence of ≥2 vaginal pathogens in which both pathogens are contributing to clinical syndrome or even if not responsible require mandatory therapy for both pathogens, given their pathogenic potential.

Table 3 Types of mixed infections

A.	Independent: two infections appear together by chance alone. Presence of one does not affect risk of getting the other. Signs and symptoms of each appear. Treatment for both is required.
B.	Dependent: two infections either positively or negatively affect (1) risk of acquisition (either directly as part of underlying ecology or biological mechanisms or indirectly because treatment of one increases risk of other); (2) clinical presentation (signs and symptoms); (3) treatment; (4) potential for sequellae.

The concept of mixed vaginitis has become relevant because of therapeutic considerations in selecting antimicrobial agents to treat symptomatic vaginitis. Combination therapy is indicated for confirmed mixed infections and wherever physicians are uncertain of causation, but severe symptoms require administration of two drugs before diagnostic tests are available. For several decades, the Federal Drug Administration in the U.S. has opposed drugs that include or combine more than one antimicrobial agent; that is, combination antimicrobial products are not permitted. The decision to disallow combination therapy was based, first of all, upon the principle of minimizing empirical or "guess-based" therapy, with multiple antibiotics in a single preparation targeting multiple potential pathogens. This regulation aimed at encouraging clinical efforts to reach the correct diagnosis and selection of a single appropriate agent directed at the pathogen responsible for the clinical syndrome. Avoiding the unnecessary use of antibiotics is also cost saving and associated with reduced toxicity, side effects, and risk of drug resistance development. Accordingly, the FDA policy has remained in force for several decades. At the time, little consideration was given to the possibility or frequency of mixed infections. In fact, there remains an extraordinary paucity of data measuring the frequency of mixed vaginitis episodes.

To this uncertainty must be added sequential mixed infections in which coinfection exists initially, but with only one pathogen causing symptoms. However, with therapeutic eradication of the dominant pathogen, the clinical picture alters, due to the sequential emergence of the second pathogen. The two consecutive clinical syndromes are often quite distinct and easily diagnosed and are often separated by days or weeks of an absence of symptoms and signs. This

phenomenon of consecutive mixed infection is best described with BV and VVC. During the initial presentation, symptoms and signs of BV alone are evident in spite of positive *Candida* cultures; however, after antibacterial therapy and disappearance of BV manifestations, women return with new symptoms due to VVC, often misdiagnosed as a relapse of BV and incorrectly treated as such. Given the appearance of coinfection at this initial presentation, it may be prudent, in selected women only, to use a combination of antimicrobials to prevent the inevitable second episode. How to select this at-risk subpopulation requires further consideration.

What Is Known About the Epidemiology of Coinfecrtions and Mixed Vaginitis?

The frequency with which mixed infections occur depends, first, upon definition and, second, on the population of women studied [9–14]. Most reports do not distinguish between mixed vaginitis and coinfection with known vaginal pathogens. There are no population-based studies describing the epidemiology of mixed vaginitis. If one includes the cervical, but not strictly vaginal, pathogens *C. trachomatis* and *N. gonorrhoeae,* higher frequencies of both coinfection and mixed infection are reported in women examined in sexually transmitted disease (STD) clinics [9, 15]. Likewise, the presence of *T. vaginalis* is linked strongly, but not exclusively, to women seen in STD clinics. Most epidemiologic studies have been performed in symptomatic women seen in STD or referral clinics, resulting in a major accrual bias, and in no way reflect epidemiologic numbers seen in low-risk women. In addition, although recent vaginal microbiome studies are reported in pregnant and nonpregnant women, one problem is that studies fail to correlate symptoms with microbe presence.

Unfortunately, attempts at measuring the epidemiology of mixed vaginitis are further complicated by inadequate diagnostic testing [3, 7, 16]. With regard to *Candida* species infections, most epidemiologic studies determined the presence of *Candida* by microscopy (NaCl and 10 % KOH) only. Microscopy as a diagnostic method is notoriously insensitive, and at least a quarter to a third of women with symptomatic VVC will have negative microscopy and positive conventional cultures [16]. In addition, in the hands of inexperienced microscopists, numerous false positive yeast results occur with negative matching yeast cultures. Patel et al. reported that in a moderately large series of symptomatic women, only 36 % had laboratory-confirmed infections [13].

In performing a literature review to assess the occurrence and frequency of mixed vaginitis, it is apparent that most investigators report coinfection rather than mixed infection. In a large culture- and microscopy-based review, Kent reported mixed infections in 15 %–20 % of diagnosed episodes but failed to separate mixed infections from coinfections. Similarly, Goel et al. reported that 30 % of 40 HIV-positive women had mixed infections [11]. Literature reports of coinfections in symptomatic women vary from 5 % to 30 % [2, 6, 8, 9, 11, 12, 17–19]. On the lower side, using traditional microscopy and culture, Donders et al. reported that among 142 women with culture-confirmed recurrent VVC, only 6.3 % had simultaneous BV, with a total of 13.3 % further diagnosed on long-term follow-up [20]. Most studies, however, reported coinfection of vaginal pathogens in approximately 30 % of women [2, 6, 8, 18, 19]. More recently, Rivers et al. reported their experience in an STD clinic and attempted to identify true mixed infections. They found BV in 72.3 % of presenting symptomatic women, in whom one third had vaginal *Candida* species cultured with an overall prevalence of 15.7 % of VVC, but a notably mixed infection reflecting a dual contribution of pathogens was present in only 4.4 % of symptomatic women [21•]. Similarly, in the Wayne State University Vaginitis Clinic, Sobel in 2011 found that of 137 women with acute symptomatic BV diagnosed by Amsel criteria, 18.2 % of the women had a positive *Candida* spp. culture. In 200 episodes of BV, overall positive *Candida* cultures were found in 13.5 %, and mixed infection, defined as coinfection plus symptoms and signs of both entities, was present in only 10/200 (5 %) of the women evaluated (unpublished data).

DNA homology laboratory testing (Affirm®, Becton Dickenson Co.) of large numbers of vaginal swabs obtained from symptomatic women revealed vaginal coinfection in 10 %–16 % [22–24]. Similarly, a recent analysis of 28,100 tests performed at the Detroit Medical Center University Laboratory in 2010 and 2011 reported coinfection in 15 % of the women tested, most frequently BV pathogens and *Candida* species.

Using PCR methodology, coinfection rates are even higher. Among 5,000 vaginal swab samples tested at Medical Diagnostics Laboratories (Hamilton, NJ) for *T. vaginalis*, *Candida* spp., and two BV-associated organisms, *G. vaginalis* and *Atopobium vaginae*, the coinfection rate was 17.8 %. *T. vaginalis*, *Candida spp.*, *G. vaginalis*, and *A. vaginae* individual positivity rates were 3.5 %, 29.2 %, 45.5 %, and 38.3 %, respectively.

Among *T. vaginalis* PCR-positive swabs, 70.1 % were also PCR positive for *G. vaginalis* and 75.1 % positive for *A. vaginae.* Hence, approximately 70 % of women with trichomoniasis were PCR positive for BV organisms. Analysis of swabs PCR positive for *Candida* spp. found that 48.3 % were also PCR positive for *G. vaginalis* and 39.1 % positive for *A. vaginae*. Overall, *Candida* coinfection was

present in 15.6 % of the total samples that were PCR positive for any of the aforementioned pathogens.

Undoubtedly, coinfection with BV organisms and *T. vaginalis* is most frequent [21•]. Women so infected present with a malodorous discharge and high vaginal pH, reflecting a likely mixed infection. Recently, in a study of HIV-positive women who were *T. vaginalis* infected, the rate of BV was 64 %, also supporting the aforementioned DNA homology and PCR data [25]. Of note, coinfection with BV was associated with early antitrichomoniasis failure following single-dose metronidazole therapy, but not for multiple-dose regimens [25].

Discussion

Although vaginal infections are an extremely common cause of vulvovaginal symptoms, little information is available on the prevalence of mixed infections, especially VVC and BV. In part, this is the consequence of widespread self-diagnosis and self-treatment with OTC antimycotic agents. Furthermore, caregivers often treat women empirically, without confirmatory tests [7].

The coexistence of BV and trichomoniasis has been poorly documented, but the limited reports available indicate that coinfection due to these pathogens is extremely common [21•, 22, 25, 26]. Our findings are consistent with those of Moodley et al. that showed a nonlinear relationship between *T. vaginalis* and vaginal flora among African HIV-positive and -negative women [26]. In part, this is a function of common or shared sexual transmission dynamics. On the other hand, little is known about pathophysiological vaginal conditions in infections that either enhance or, less likely, inhibit pathogens of the other entity [27]. Trichomonads appear to benefit from the high pH and anaerobic environment that accompanies BV [27]. Moreover, *T. vaginalis* infection may create an environment that is conducive to a shift away from normal and, hence, contribute to development of BV [22]. From a therapeutic point of view, the unrecognized presence of BV in women with vaginal trichomoniasis may, at first glance, appear irrelevant, since recommended nitroimidazole therapy, usually administered systemically, is predictably also likely to be effective against BV. Data on drug efficacy are entirely unavailable for these mixed infections apart from the study of Gatski et al. [25]. The interactions of these two processes are, therefore, fertile areas for further study [28].

In contrast, mixed infections due to BV and VVC have recognized therapeutic implications. As was mentioned earlier, the prevalence of *Candida* vaginal colonization in women with symptomatic BV varies considerably, with a range that peaked at 74 % in a cohort of women with recurrent BV [29]. It is not standard care for a woman with symptomatic BV who is also colonized with *Candida* spp. to be treated simultaneously with an antimycotic agent in addition to antibacterial therapy [30]. Polytherapy should be based on the available history of past vulnerability to antibiotic-induced VVC [31].

The incidence of microscopy-defined BV among women with symptomatic VVC varies considerably in reported studies, ranging from 3 % to 27 %, depending upon the population studied [20, 30]. Individual signs and symptoms have shown only modest benefit in recognizing mixed BV/VVC infections [21•]. The complaint of pruritus in a patient with BV should alert practitioners to the high likelihood of coexistent vaginal *Candida* infection. Similarly, in women diagnosed with BV, a thick, curdy, or clumpy discharge, as well as the presence of vulvovestibular signs of inflammation and vaginal soreness, should suggest a mixed infection [21•]. In contrast to BV/VVC pathogen coinfection, mixed infections require a therapy directed at pathogens of each entity.

It is likely that as practitioners move toward laboratory-based diagnosis, including antigen detection, DNA probes, and PCR, as opposed to point-of-care microscopy and pH determination, recognition of the coexistence of multiple pathogens will only increase. This phenomenon will increase demand for polytherapy using multiple antimicrobials in separate or combined preparations, although many countries have banned the availability of combination antimicrobial products for use in vaginitis. Polytherapy, while appropriate for mixed vaginitis, is unnecessary for coinfection involving *Candida* species.

Nevertheless, consideration for polytherapy is appropriate for a consecutive mixed infection in which symptomatic VVC follows shortly after antimicrobial therapy for BV or trichomoniasis in which *Candida* colonization was present at the time that the initial vaginal symptoms were diagnosed [28]. The high prevalence of consecutive symptomatic VVC in patients following treatment of BV indicates the considerable risk accompanying *Candida* colonization or coinfection, which is potentially preventable by the addition of antimycotics to antibacterial therapy at the time of initial bacterial infection [28].

In summary, mixed infections, although largely ignored and poorly studied, appear uncommon in contrast to frequent pathogen coinfection, particularly involving BV and VVC as well as BV and trichomoniasis. Coinfection with two or more vaginal pathogens justifies consideration in selecting appropriate antimicrobial therapy. It is essential to improve and make available diagnostic modalities that facilitate recognition of the coexistence of multiple pathogens in determining whether antimicrobial combination regimens should be recommended.

Disclosure No potential conflicts of interest relevant to this article were reported.

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