Questions remain regarding the presence of fungal species biofilm in women with vulvovaginal candidiasis

Check for updates

TO THE EDITORS: In the insightful publication by Swidsinski et al,[1] the authors address important questions regarding the presence of vaginal biofilm in cases of vulvovaginal candidiasis (VVC). They conclude following evaluation of vaginal biopsies that lesions are primarily polymicrobial and do not contain biofilm.

In a related study by our group, demonstrating that *Candida albicans* actively forms biofilm on the vaginal mucosa in the mouse model of VVC,[2] similar questions regarding clinical VVC were raised. While we applaud the authors for designing a clinical study that addressed the issue through vaginal biopsies, we believe it important to point out some limitations to the study that stress caution in the interpretation of the results.

First, because the biopsies were all taken from the middle side wall, and without colposcopy, areas of discontinuous biofilm formation might not have been sampled. Second, although infected areas did appear to be sampled based on the level of invasion and presence of mycelium/hyphae, surface biofilm could have been disrupted or dislodged with biopsy removal and sample preparation. Third, the biopsy sections were not evaluated for fungal extracellular matrix, the hallmark of *Candida* biofilm formation, or assessed by confocal microscopy for high-resolution serial sectioning that provides 3-dimensional reconstruction of thick microbial biofilm structures.[2]

As an alternative argument in agreement of the interpretations/conclusions made, there is evidence for less frequent antifungal resistance in recurrent VVC (RVVC) than in other forms of recurrent candidiasis.[3] Less antifungal resistance may reflect reduced biofilm presence. In addition, erythema (redness) is a common documented sign of VVC/RVVC.[4] This sign of infection is synonymous to the erythematous form of oral candidiasis and not the pseudomembranous form that presents as white plaques that visually reflect the presence of biofilm.[4]

Conversely, another common sign of VVC/RVVC is a cottage cheese–like discharge that is considered a mix of *Candida*, dead epithelial cells/leukocytes, and vaginal secretions.[4] As such, parts of the discharge could represent biofilm sloughed from the vaginal wall. Swidsinski et al[1] did not evaluate discharge in their study.

In conclusion, while the interpretations made by the authors regarding the histopathology of VVC were correct based on the study design and results obtained, the limitations of the study and inability of the methods to specifically detect biofilm elements, stress caution relative to data overinterpretation. Hence, important questions remain regarding the presence of biofilm or role of biofilm formation in VVC. ■

Mairi C. Noverr, PhD
Paul L. Fidel Jr, PhD
Department of Oral and Craniofacial Biology
Center of Excellence in Oral and Craniofacial Biology
School of Dentistry
Louisiana State University Health Sciences Center
1100 Florida Avenue
New Orleans, LA 70119
pfidel@lsuhsc.edu

The authors report no conflict of interest.

REFERENCES

1. Swidsinski A, Guschin A, Tang Q, et al. Vulvovaginal candidiasis: histologic lesions are primarily polymicrobial and invasive and do not contain biofilms. Am J Obstet Gynecol 2019;220:91.e1–8.
2. Harriott MM, Lilly EA, Rodriguez TE, et al. *Candida albicans* forms biofilms on the vaginal mucosa: implications for the pathogenesis of vaginal candidiasis. Microbiology 2010;156:3635–44.
3. Lynch ME, Sobel JD, Fidel PL Jr. The role of antifungal drug resistance in the pathogenesis of recurrent vulvovaginal candidiasis. J Med Vet Mycol 1996;34:337–9.
4. Fidel PL Jr. *Candida albicans*: from commensal to pathogen. In: Tannock G, ed. Medical importance of the normal microflora. London: Kluwer Academic Publishers; 1999; p 441–476.80.

 https://doi.org/10.1016/j.ajog.2019.04.017

REPLY

Check for updates

We appreciate the thoughtful comments of Noverr and Fidel as to the findings in our recent publication evaluating the presence of *Candida*-associated biofilm in women with acute vulvovaginal candidiasis (VVC).[1] The study produced 2 conclusions: (1) the extensive and previously unreported human vaginal mucosal invasion and infiltration by *Candida* microorganisms as well as the clinical consequences of tissue invasion; and (2) failure to document using a well-described and widely used technique of fluorescent in situ hybridization with ribosomal gene-based probes, the presence of microscopic biofilm, containing *Candida* species microorganisms.

The latter finding is also of clinical significance in that no justification was forthcoming for utilizing biofilm busters as

part of the therapy of acute VVC, especially in patients with recurrent VVC.[2]

Noverr and Fidel are concerned about the vaginal site from which biopsies were taken, the VIZ mid-side wall. This is the traditionally preferred site for obtaining vaginal yeast culture, recognizing the macroscopic appearance similarity of the vagina through 360° with regard to appearance, histology, and microbiome. In addition, there is a lack of access to the vaginal floor and ceiling because of the speculum blades used in examination. Clearly biofilm could be disrupted in the biopsy process, but to be absent to the extent it was, makes this extremely unlikely, and bacterial biofilm was clearly apparent and retained. It is true that extracellular matrix was not stained for.

It is critical to emphasize that one should not confuse macroscopic biofilm evident on catheters and in plastic wells containing *Candida* populations containing extracellular matrix with microscopic biofilm evident only in histopathological vaginal sections (eg, bacterial vaginosis), which is invisible to the naked eye.

Clinicians are experienced in separating the grayish white frothy vaginal discharge characteristic of BV from the clumpy white discharge, sometimes adherent and confluent, typical of VVC. The macroscopic white plaques seen in VVC, reflecting large populations of hyphae producing *Candida* microorganisms together with bound epithelial cells and debris, do not reflect or constitute biofilm. Discharge in our study is entirely irrelevant.

We agree that antifungal drug resistance has been infrequent in the past in women with recurrent VVC because of *C albicans*; however, the frequency has increased significantly as a function of fluconazole drug exposure[3] and unrelated to biofilm existence. Resistance may also emerge as a consequence of deep mucosal persistence of yeast organisms, an observation that deserves further study. ■

Alexander Swidsinski, MD
Moleculargenetic Laboratory for Polymicrobial Infections und Biofilms
CCM, Charité, Universitätsmedizin Berlin, Hufelandweg 5
10117 Berlin, Germany
alexander.swidsinski@charite.de

Jack Sobel, MD
Wayne State University School of Medicine
Detroit, MI

The authors report no conflict of interest.

REFERENCES

1. Swidsinski A, Guschin A, Tang Q, et al. Vulvovaginal candidiasis: histologic lesions are primarily polymicrobial and invasive and do not contain biofilms. Am J Obstet Gynecol 2019;220:91.e1–8.
2. Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol 2016;214:15–21.
3. Marchaim D, Lamanek L, Bheemreddy S, et al. Fluconazole-resistant Candida albicans vulvovaginitis. Obstet Gynecol 2012;120:1407–14.

 https://doi.org/10.1016/j.ajog.2019.04.018

Years of unjustified hypoestrogenism, fear, and stress will not improve the management of chronic pelvic pain!

TO THE EDITORS: Agarwal et al[1] should be congratulated for emphasizing that patients with severe chronic pelvic pain should be managed actively. Indeed, years of inadequate treatment, with the assumption that this pain is normal, is deeply frustrating for these patients. Chronic pain may have significant negative impact on a patient's quality of life, resulting in central sensitization, loss of self-confidence and trust in physicians, and making long-term management more difficult.

Some of these women have severe or deep endometriosis that may be identified clinically or with imaging techniques. Others may have superficial disease, which could be confirmed at laparoscopy, although this should not be the first option in teenagers. Even minimally invasive surgery is too invasive to manage minimal endometriosis, which is not always progressive and may heal during medical treatment or even spontaneously.[2]

The presumption of endometriosis should not be mandatory for the physician to propose adequate treatment of severe chronic pelvic pain in young patients without obvious or confirmed endometriotic lesions. Many of these patients do not have and will never have endometriosis. The menstrual disorder of teenagers (MDOT) study reported that almost 30% of teenagers thought that something was wrong with their period, and 21% reported severe pain and 47% moderate pain.[3] However, the prevalence of endometriosis is about 10% among women of reproductive age.

Overdiagnosing the disease using clinical criteria because a noninvasive diagnosis test is not available will have severe consequences. Treatment of "a supposed endometriosis" with high-dosage progestins or gonadotropin-releasing hormone agonist will likely result in years of unnecessary hypoestrogenism. Young patients will experience years of unjustified fear and anxiety about probable infertility induced by a "possible mysterious chronic disease" that cannot be cured. Fear will likely worsen the symptoms of these young patients as adolescents' pain involves a significant psychosomatic component.