

REPLY

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 exposure³ 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. ■

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