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## **Pathogenic biofilm in recurrent vaginitis and cystitis**

### **Introduction**

Pathogenic biofilms are the emerging frontier of research and clinical strategies to face the challenging issue of increasing antibiotic resistances. In urology and gynecology, recurrent cystitis and vaginitis represent an important part of daily medical consultations. The failure of a clear diagnosis is often frustrating both for patients and physicians.

The aim of the presentation is to concisely review the evidence on pathogenic biofilm and to consider new non antibiotic strategies of intervention.

### **Structure of biofilms and their scenario in humans**

Biofilms are composed by germs aggregated within a self-produced matrix. About 15% of biofilms composition is a complex assembly of synergistic and often pathogenic microorganisms, secreting approximately 85% of adhesive polysaccharides (Extracellular Polymeric Substance, EPS). The biofilm has a primitive circulatory system. The structured communities of bacterial and fungal cells are enclosed in a self-produced polymeric matrix and adhere to a living or inert surfaces, such as medical devices.

Biofilm are involved in diseases in diverse medical specialties, including but not limited to: endocarditis, recurrent bronchial or lung infections, rhinosinusitis, otitis media, prostatitis, gastrointestinal bowel disease, cystitis and vaginitis, underlying a general microbiologic aggressive and survival-oriented strategy.

In urogynecology, the recent increase of bacterial resistance and microbial aggression suggests a connection with the indiscriminate use of antibiotics and pathogenic biofilms' formation in vagina and in urothelium. Therefore, an innovative approach is necessary to avoid the escalation in antibiotic use and antibiotic resistances in urogynecology.

### **Pathogenic biofilms in the etiology of recurrent vaginitis ad cystitis**

In the urogynecological field, recidivism and chronic infections can be explained through the theory of biofilms. In the vagina and in the urothelium biofilms can be respectively extracellular and intracellular.

In both cases, in the deep layer of biofilms, with a low presence of oxygen and nutrients, pathogens live in a quiescent state as **persistor cells** (PC). They are resistant to antibiotics because they are in a phenotypic and metabolic protected state. The deep location of PC also ensures bacterial cells resistance to innate and cell mediated immune host defenses, but always ready to re-attack the host. The persistence of vaginitis and cystitis, with alternate phases of bacteriuria, are justified through the detachment of a persistent bacterial inoculum from a mature biofilm that colonizes other venues, until systemic invasion. Diagnosis and treatment of biofilms may be more efficient if compared to the antibiotic therapy, often ineffective in the long term.

The knowledge of biofilms can help physicians to explain:

1. incomplete or absent response to prolonged antibiotic therapy;
2. high presence of comorbid forms of antibiotic-resistant infections and disease;
3. the increasing bacterial resistance to immune effectors;
4. the infection's tendency to become chronic.

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### **Extracellular biofilms**

They usually grow close to the vaginal vestibule, and along the vaginal wall. They reside near apical cell surface of the vaginal mucosa and protrude towards the cavity. Extracellular biofilms are characteristic of the surface of different mucous or waste materials, such as medical devices (vaginal contraceptive ring, pessary, intrauterine devices, subcutaneous implants, catheters). In urogynecology they give rise to antibiotic-resistant chronic polymicrobial infections and explain recidivism and comorbidities between recurrent cystitis and vulvar vestibulitis with provoked vestibulodynia.

### **Intracellular biofilm**

They reside inside the urothelium that covers the inner bladder/wall bladder. They are characterized by a specific pathogenic strain of Uropathogenic Escherichia Coli (UPEC), carrier of the antigen K. This strain is responsible for 75-85% of recurrent cystitis and intracellular biofilm formation. Intracellular bacteria are enclosed in a polysaccharide matrix and enveloped by a protective shell of uroplakins. Intracellular biofilms are a reservoir of micro-organisms immune to antibiotics and to immune system effectors. Mimicking what happens in the outer world, they are equivalent of intracellular “terrorists” difficult to be reached by antibiotics and the host’ immune system, and yet capable of progressive tissue damage and inflammation. They cause chronic inflammation of the bladder wall, which can evolve to cause a “painful bladder syndrome”, and “interstitial cystitis”.

### **Comorbidity in urogynecology**

Recent evidence stresses the synergism and the increasing comorbidity between recurrent cystitis, recurrent vaginitis, introital coital pain and its leading etiological counterpart, that is **provoked vestibulodynia** (PVD). It was formerly defined as vulvar vestibulitis. Comorbidity in urogynecology also supports the need of a parallel vision to address recurrent vaginitis and cystitis and sexual comorbidities: introital coital pain (“introital dyspareunia”) and postcoital cystitis (cystitis that are usually complained of 24 to 72 hours after intercourse).

### **Non antibiotic therapeutic strategies**

Aggressiveness of pathogenic biofilms can be reduced with a multimodal approach:

- modulation and empowerment of intestinal physiologic biofilm, through appropriate diet and probiotics;
- maintenance of optimal vaginal ecosystem with at least topical, vaginal, estrogenic treatment;
- reduction of pathogenic vaginal biofilms through topical treatments with N-acetyl–cysteine, probiotics, D-mannose;
- relaxation of the pelvic floor, if hyperactive, with electromyographic biofeedback and hands-on physiotherapy;
- reduction of UPEC aggressiveness in the bladder with oral D-mannose and cranberry at adequate doses;
- adequate, consistent and persistent modifications of inappropriate life-styles.

Data on effectiveness will be finally presented.