

A. Graziottin P.P. Zanello

## **Recurring vaginitis and cystitis: which role for pathogenic biofilms?**

Abstract of the Invited Lecture presented at the 22nd World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI), Budapest, Hungary, September 17-20, 2015

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Recurrent cystitis and vaginitis are a prominent part of daily medical consultations in urology and gynecology. The difficulty in addressing recurrences with an effective therapeutic strategy is increasingly frustrating, both for patients and physicians. Despite the failure in reducing the aggressiveness of bacterial pathogens especially in the uro-genital tract, there is a limited awareness of the clinical importance of polymicrobial biofilm in infectious processes and in their escalating drug-resistance, which suggests a key connection with the parallel growth of antibiotics' medical prescriptions (Kamenski et Al 2012; Ruef 2005).

Pathogenic biofilms are the emerging frontier of research and clinical strategies to face the challenging issue of increasing antibiotic resistances. The evidence on pathogenic intracellular or extracellular biofilm, usually in the bladder or in vagina respectively, must be considered to undertake new prophylactic non antibiotic strategies of intervention (Graziottin et Al 2014).

Biofilms are composed of different pathogenic micro-organisms (about 15%), such as *Escherichia coli*, *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, group B streptococci, *Enterobacter*, *Pseudomonas Aeruginosa*, *Staphylococcus Saprophyticus*, *Staphylococcus Aureus*, *Chlamydia Trachomatis*, *Mycoplasmas*, *Candida Spp*, *Mycobacterium tuberculosis*, originating from bowel flora, aggregated within a self-produced matrix (Extracellular Polymeric Substance, EPS, 85%).

The complex assembly of synergistic, and often pathogenic, micro-organisms adhere to a living or inert surfaces, such as medical devices. Inside the biofilm, micro-organisms have a low metabolic profile and higher resistance to environmental damaging factors, immune system and antibacterial substances, both present in the environment and in the host organism during infections (Graziottin et Al 2014).

Inside the biofilm, the amplified bacterial resistance has three basic mechanisms:

1. physical-chemical resistance to antibiotics, such as ciprofloxacin and aminoglycosides;
2. metabolic resistance (slow metabolic cell profile);
3. genetic resistance (plasmids transfers) (Lanwermeier et Al, 2014).

In gynecology, pathogenic biofilms can explain the incomplete or absent response to prolonged antibiotic therapy, the high presence of comorbid forms of antibiotic-resistant infections and diseases, the increasing bacterial resistance to immune effectors and the vaginal infection's tendency to become chronic (Swidsinski et Al 2013). This evidence is clinically confirmed by positive or negative bacteriuria at alternate phases, and parallels the same pathophysiologic mechanisms operating in recurrent nose, sinus, bronchial or lung infections, thus underlying a general microbiologic aggressive and survival-oriented strategy.

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Recent evidence stresses the synergism and the increasing comorbidity between recurrent cystitis, recurrent vaginitis and introital coital pain. Comorbidity in urogynecology also supports the need of a parallel vision to address recurrent vaginitis and cystitis (Salonia et Al 2013).

**An innovative preventive, prophylactic and therapeutic strategy** is currently focused on preventing mucosal bacterial adhesion and biofilm formation. These **alternatives to antibiotics** can be found in **bioidentical** substances, such as D-mannose, which reduces the E. Coli aggressiveness and its ability to adhere and attack vaginal and urothelial cells, while exhibiting reparative potentials as well.

D-mannose is metabolically inert: 90% of it is excreted intact in the urine where it exerts its main preventive and therapeutic action. Its use is safe in pregnant women, in children and in the elderly (**Box 1**) (Graziottin et Al 2014). D-mannose, when integrated in a multimodal approach, may help patients to prevent recurrent vaginitis and cystitis.

#### **Box 1. D-mannose: the biological basis of its efficacy**

**Exogenous D-mannose** is extracted from birch and larch wood. It is a **bioidentical substance, as it has the same structure of endogenous D-mannose**, a low molecular weight monosaccharide, a normal component of different biological molecules on cell surfaces. When ingested, D-mannose is sparsely metabolized by human cells and eliminated unchanged through the urine.

D-mannose has an high affinity to lectins of *Escherichia coli* and to many other fimbriated bacteria. The use of D-mannose seems to be a winning strategy in both prophylaxis and interventions in recurrent urinary tract infections (rUTI) and vaginitis, as it prevents bacterial adhesion and facilitates the mechanical detachment (Jiang et Al 2012; Kranjčec et Al 2013).

Exogenous D-mannose **mimics, surrogates and integrates a protective kidney protein**, rich in D-mannose residues, **the Tamm-Horsfall protein**, usually defective in women more vulnerable to recurrent cystitis (Pak et Al 2001). D-mannose prevents *E. coli* cell receptors to adhere to bladder and vaginal epithelium, first stage of cystitis, vaginitis and biofilm formation. D-mannose also favors the restructuring of damaged mucosa, especially of the vagina, thus ensuring greater protection from subsequent bacterial and mechanical damage (Alton et Al 1998; Panneerselvam et Al 1997).

#### **References**

G. Alton, M. Hasilik, R. Niehues, K. Panneerselvam, J.R. Etchison, F. Fana, H.H. Freeze  
Direct utilization of mannose for mammalian glycoprotein biosynthesis  
Glycobiol 1998; 8 (3): 285–295

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Cistiti e vaginiti recidivanti: ruolo dei biofilm e delle persister cells. Dalla fisiopatologia a nuove strategie terapeutiche

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Min. Ginecol 2014, 66;(5) 497-512

X. Jiang, D. Abgottspon, S. Kleeb, S. Rabbani, M. Scharenberg, M. Wittwer, M. Haug, O. Schwardt, B. Ernst

Antiadhesion therapy for urinary tract infections--a balanced PK/PD profile proved to be key for success

J Med Chem 2012; 55(10):4700-13

G. Kamenski, G. Wagner, S. Zehetmayer, W. Fink, W. Spiegel, K. Hoffmann

Antibacterial resistances in uncomplicated urinary tract infections in women: ECO•SENS II data from primary health care in Austria

BMC Infect Dis. 2012 Sep 18;12:222

B. Kranjčec, D. Papeš, S. Altarac

D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial

World J Urol 2013; 32(1):79-84

K.S. Lanwermeyer, C. Xi, N.S. Jakubovics, A.H. Rickard

Mini-review: Microbial coaggregation: ubiquity and implications for biofilm development

Biofouling. 2014 Nov;30(10):1235-51

J. Pak, Y. Pu, Z.T. Zhang, D.L. Hasty, X.R. Wu

Tamm-Horsfall protein binds to type 1 fimbriated Escherichia coli and prevents E. Coli from binding to uroplakin Ia and Ib receptors

J Biol Chem 2001; 276(13):9924-30

K. Panneerselvam, J.R. Etchison, H.H. Freeze

Human Fibroblasts Prefer Mannose over Glucose as a Source of Mannose for N-Glycosylation

J Biol Chem 1997; 272 (37) 23123–23129

C. Rued

Clinical relevance of antibiotic resistance in obstetrics and gynecology

Gynakol Geburtshilfliche Rundsch 2005; 45(1):19-27

A. Salonia, M.C. Clementi, A. Graziottin, R.E. Nappi, F. Castiglione, M. Ferrari, U. Capitano, R. Damiano, F. Montorsi

Secondary provoked vestibulodynia in sexually-active women with recurrent uncomplicated urinary tract infections

J Sex Med 2013; 10 (9): 2265-73

A. Swidsinski, H. Verstraelen, V. Loening-Baucke, S. Swidsinski, W. Mendling, Z. Halwani

Presence of a polymicrobial endometrial biofilm in patients with bacterial vaginosis

PLoS One 2013; 8(1):e53997