

Recurrent Urinary Tract Infections (R-UTIs): a new vision in gynaecology

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Recurrent Urinary Tract Infections (R-UTIs) are common in postmenopausal women. Recurrence is defined as three or more episodes in 12 months or two or more episodes in 6 months. Post-coital R-UTIs may represent the sole or predominant pattern of recurrence. Pathophysiology of R-UTIs is complex. Multiple factors may play a role in determining the persistence of Lower Urinary Tract Symptoms – LUTS, and the recurrence of cystitis. Understanding the whole scenario is of crucial importance in designing a personalized treatment, whereas the use of multiple courses of antibiotics often results to be both ineffective and potentially harmful. The following *predisposing, precipitating and maintaining factors* should be considered, investigated, and treated.

A. PREDISPOSING FACTORS

The metabolic factor: increasing evidence suggests that insulin-treated diabetes is a powerful predisposing factor for R-UTIs (OR=3.4). Controlling diabetes is a preliminary measure to reduce R-UTIs.

The intestinal factor: an altered intestinal flora may lead to the overgrowth of enterobacteriaceae, that are the causative agents of the vast majority of R-UTIs, more so after the menopause. The Irritable Bowel Syndrome (IBS) with the associated hyperactive mast-cells in the intestinal mucosa and the increased passage (“translocation”) of intestinal germs through the intestinal cells is a key predisposing factor to R-UTIs, frequently comorbid with IBS itself. Constipation, that tend to worse with age and menopause, is another important intestinal predisposing factor. The minimalistic approach of using antibiotics to treat R-UTIs, without addressing the complexity of R-UTIs’ pathophysiology, may alter the intestinal flora, predisposing to fungal and bacterial overgrowth.

The urethral factor: the urethral mucosal, sub-mucosal, and muscular layers should ensure a good “sealing effect” of the urethral lumen, thus preventing ascending infections during intercourse. This protective mechanism is partially oestrogen and partially androgen dependent, and may become defective after menopause. The bladder, the urethra and its surrounding structures are rich in estrogen receptors and there are demonstrable physiological and anatomical changes that occur around and immediately after the menopause. Increasing evidence suggests that the loss of estrogens is a causative predisposing factor in postmenopausal R-UTIs.

The bladder factor: the urothelium is coated by Glycosaminoglycans (GAG’s) and Proteoglycans. This functional a-cellular layer, referred to as “bladder coating”, ensures the impermeability of the bladder surface to urine’s ions and bacteria. A defective bladder coating may lead to the passage of urine’s constituents and bacteria across the urothelial barriers, till to reach the interstitial space. Mast-cells activation and its consequent pro-inflammatory cascade of events may follow to bladder’s barriers violation. A mast-cell mediated neurogenic inflammation, both peripheral and central, can give rise to neurogenic pain, as it happens in the Bladder Pain /Painful Bladder Syndrome, and in the Interstitial Cystitis.

The bacterial factor: Uropathogenic *Escherichia Coli* – UPEC is responsible for 85% of R-UTIs, whereas 15% is due to *Proteus Mirabilis*, *Klebsiella*, *Enterobacter*, *Enterococcus Fecalis*, *Pseudomonas Aeruginosa*, *Staphylococcus Saprophyticus*, *Staphylococcus Aureus*, *Chlamydia Trachomatis*, *Mycoplasmas*, *Candida Spp*. Recurrent cystitis in the fertile age are powerful predictors of postmenopausal R-UTI (OR=6.9).The wide and repeated use of antibiotics, often on an empirical basis, is leading to a an extraordinarily quick and much worrying onset of antibiotic-resistance. Furthermore, Uropathogenic *Escherichia Coli* – UPEC is also able to adopt Intracellular lifestyles and immune evasion strategies and direct a complex, intracellular cascade that shelters bacteria from host defenses, thus leading to persistent bacterial residence within the epithelium, via the development of biofilm-like intracellular bacterial communities – BICs.

The pelvic floor factor: pelvic floor muscles may react to tissue and neurogenic inflammation becoming dysfunctional and tense. The pelvic floor overactivity contributes in creating and maintaining pelvic pain and LUTS. The hyperactive elevator ani may contribute to the mechanical trauma of the urethra when intercourse is accepted without adequate lubrication and genital congestion.

The hormonal factor: loss of estrogens (and partially of testosterone) deprives the vagina, the urethra and the cavernosal bodies of a key protective factor for all the tissue components (vascular, mucosal, immunitary, muscular, nervous) and for a normal sexual response. Estrogens are also essential in maintaining the normal vaginal ecosystem, with the prominent Lactobacilli, a powerful defense towards saprophytic colonic germs.

B. PRECIPITATING FACTORS

The sexual factor: on average 60-70% of R-UTI are post-coital. Recent data suggests a 3 to 4-fold increase in risk of symptomatic UTI on the second day after sexual intercourse. This vulnerability increases in untreated menopause, when lack of estrogens prevents the usual congestion of the periurethral vessels, that in normal conditions protects the urethra from the mechanical trauma of intercourse. Loss of desire and inadequate mental and genital arousal may further contribute to the urethral and bladder vulnerability to intercourse and R-UTIs.

The environmental/cold factor (cystitis “a frigore”): a sudden change in the environmental temperature (because of bathing in cold water, or moving from hot areas to air-conditioned rooms) may precipitate R-UTIs, more so in subjects with a previous history of UTIs.

C. MAINTAINING FACTORS

The diagnostic omission of the complex pathophysiology of R-UTIs is the most important predictor of further recurrences. Many women tend progressively to avoid intercourse to prevent further R-UTIs, given the strong link with the sexual activity, with a major loss in term of personal and couple’s happiness and sexual satisfaction.

CONCLUSION

The lecture will discuss the pathophysiology of postmenopausal R-UTIs and address the diagnostic and therapeutic flow-chart with a pragmatic approach useful to the gynecologist in his/her daily practice.