5

# Recurrent Cystitis after Intercourse: Why the Gynaecologist Has a Say

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*"The supreme art of war is to subdue the enemy without fighting (…). The greatest commander is not the one who reports one hundred victories over one hundred battles, but the one who wins without giving battle"*

Sun –Tzu', The Art of War, 2nd century BC

Urinary tract infections (UTIs) are very frequent in women in their lifespan. UTIs rank as the third most frequent infection, after respiratory and gastrointestinal, according to Canadian data.[1] UTIs affect 13 million people yearly in the US.[2] They cause serious discomfort to women, and have a high impact on ambulatory healthcare costs, through outpatient visits, diagnostic tests and prescriptions.[3]

Cystitis is defined as a bacterial infection of the lower urinary tract, which causes both pain when passing urine, and urgency, haematuria, and suprapubic pain not associated with passing urine.[3] In women, cystitis is the most frequent clinical presentation of UTIs: 50–60% of women have at least one episode of cystitis after puberty.[4] In the majority of cases, first episodes coincide with the beginning of sexual intercourse. Comorbidity with lifelong introital dyspareunia is frequent,[5–8] but usually under-investigated and under-reported.

Recurrent urinary tract infections (R-UTIs) is defined as three or more episodes in 12 months or two or more episodes in 6 months.[1]

Uncomplicated R-UTIs associated with uropathogenic *Escherichia coli* (UPEC) are common among healthy, reproductive-aged women. Age and menopause may contribute to R-UTIs because of the urogenital involution due to the loss of oestrogens and the worsening of constipation with age. Cystitis after intercourse (post-coital cystitis [PCC]) accounts for 60% of recurrent cystitis. This form peaks in nulliparous women (or women who had caesarean section) during the fertile age. One study found that 27% of college women with their first UTI develop a second infection within 6 months of the first episode, and 27% had a second recurrence during this period.[9] Key characteristics of cystitis are summarised in Box 1 and 2. Intercourse has been shown to precipitate R-UTIs also in the 40% of postmenopausal women (OR=3.42).[10] A gender vulnerability is clear: in the adulthood, recurrent cystitis are reported in 1 woman out of 3, and 1 man out of 20.[11]

**Box 1.** Definition of cystitis

- "Cystitis" indicates the presence of infections and/or inflammation of the bladder and urethra, accompanied by urinary symptoms.
- The infection is proven when the presence of bacteriuria (conventionally, more than 100,000 forming colony germs) is demonstrated through the urine exam and urine culture.
- Inflammation of the bladder may be present also without a significant urine infection (bacteriuria). It may be triggered by mechanical trauma (intercourse, if vaginal dryness and/or a hyperactive pelvic floor are present); physical factors (cold); radiotherapy; chemotherapy; and be associated or not to bacteriuria.

**Box 2.** Symptoms and signs of cystitis

*Symptoms* of cystitis include the following:

- urgency
- increased frequency of micturition (more than seven times during the daytime)
- sovrapubic pain and sense of weight
- burning pain at micturition, with great variability across subjects
- signs of cystitis include the following: torbid urines, sometimes with an unpleasant smell; sometimes with blood ("haematuria" or "hemorrhagic cystitis")

Pathophysiology of R-UTIs is complex.[8,11–24] Multiple factors may play a role in determining the recurrence of cystitis.

Most physicians treat R-UTIs with multiple courses of antibiotics, increasing doses and prolonged time of treatment,[3,25] therefore focusing only on the aggressor(s) germs. Although generally self-limiting, treatment of UTIs with antibiotics leads to a more rapid resolution of symptoms and is more likely to clear bacteriuria, but also selects for resistant uropathogens[26] and commensal bacteria, and adversely affects the gut and vaginal microbiota, with different and relevant comorbidities.[7,27–30] Moreover, the high prevalence of R-UTIs and the worsening of the frequency pattern of PCC clearly indicate that this bladder-centred and bacteria-oriented approach, although evidence-based medicine (EBM) supported,[3,25] in the long term is ineffective for many women, potentially harmful and needs to be revised. Alternative strategies for managing R-UTIs deserve to be explored,[31] with special attention to the two key protagonists of this "biological war": the host (the woman and her biological ground where the infection takes place) and the aggressor (the germs).[11,12,19,20,24]

Objectives of this chapter are as follows:

1. to report *women's wording*, to help the gynaecologist to capture the essence of the bladder complaint and relevant comorbidities
2. to analyse the *host/woman's vulnerabilities* through the accurate detection of *predisposing, precipitating and maintaining factors* contributing to R-UTIs and specifically to PCC
3. to identify the key characteristics of the *aggressor*(s) germs
4. to indicate why and when the *gynaecologist* may effectively contribute to prevent and treat R-UTIs in women
5. to briefly design a *multimodal therapeutic strategy*, based on current evidence and clinical experience of the author; the latter is focused on addressing predisposing, precipitating and maintaining factors, as substantiated in her lifelong clinical practice in treatment of R-UTIs/PCC

## Recurrent Cystitis: Women's Wording

Listening carefully to *women's wording* helps the gynaecologist to recognise factors he/she can competently address to reduce women's vulnerability to R-UTIs.

"I had my first cystitis the night I had my first intercourse." The so-called "honeymoon cystitis" was well known to family physicians, when the young bride had to ask for help to be relieved from acute bladder pain at the beginning of her sexual life. Cystitis could be mechanically triggered by intercourse in an unexperienced woman, tense, afraid of the intercourse, with poor lubrication/vaginal dryness and/or a defensively contracted pelvic floor[5,7,32–34] and/or after repeated intercourses.

"Symptoms of cystitis gets worse the week before periods." This is reported by 10–15% of women with isolated cystitis, up to 25–28% of those who complain of comorbidity with introital dyspareunia and/or provoked vestibulodynia (PVD) (former vulvar vestibulitis)/vulvodynia.[5,7,35] The premenstrual "flares" may be triggered by the fluctuations of oestrogens increasing the degranulation of mast cells and consequent release of inflammatory molecules in the bladder wall.[28,36]

"My first cystitis was so painful! I lost a lot of blood…" Gross haematuria indicates a significant damage of the internal glucosaminoglican (GAGs) bladder coating, separating and protecting the urothelium from the urine. This may predispose to the invasion of the urothelium by *E. coli*, forming colonies of germs, the so-called "intracellular bacterial communities" (IBCs).[17,19,21,22,24,37,38]

"I have the cystitis, I take the antibiotics and I get a Candida vaginitis. I use antimycotis and after another intercourse I have a cystitis again. And now the intercourse is painful, and my vagina burns afterwards. It's a nightmare." The patient describes the negative effects of antibiotics on ecosystems (intestinal, vaginal) and the emerging of a very aggressive Candida infection in the vagina and, sometimes, in the bladder.[39,40] The recurrent Candida may contribute to PVD and dyspareunia, which is comorbid with cystitis in up to 60% of patients.[7,8]

"I have all the symptoms of a cystitis. I do the exams and the culture is negative. But if I take an antibiotic I feel a bit better. How is it possible?" Symptoms are caused by IBCs, mostly of UPEC.[17,19,21,22,37,38] The culture may be negative if the germs who get out from the cell are in small quantity (<100,000 units forming colonies, conventionally insufficient to give a positive culture), or if they are "cell wall deficient" (CWD), after a pleiomorphic mutation, and therefore not sensible to antibiotics. Antibiotics can nevertheless improve the symptoms when they attack the subgroup of *E. Coli* with the capsule, expulsed by the urothelial cells.

"I've been diagnosed with insulin-dependent diabetes since I was 12. Now, at 28, I have recurrent cystitis. I feel it gets worse when the glycaemia is higher. Is there a relationship between my diabetes and my cystitis?" Diabetes can double or triple the probability or recurrent cystitis, according to the quality of the glycaemic control, the duration of the diabetes, its being insulin-dependent and having comobidities such as retinopathy or obesity.[13,14,18,41–43]

"When I'm stressed I'm more vulnerable to get a cystitis again and bladder pain gets worse. Is it "psychogenic", as my doctors says? I'm not inventing my pain!" Stress may predispose to cystitis and worsen pain perception with different modalities: it activates the corticotrophin-releasing pathway and it facilitates the cytokine release from the mast cells, increasing the local inflammation[44]; stress-associated anxiety reduces central pain threshold with increased perception of pain; it causes pelvic floor muscles hyperactivity, narrowing of the

vaginal entrance, inhibited lubrication, with introital dyspareunia and increased vulnerability to the mechanical trauma of intercourse.[7]

"I had cystitis since my adolescence. After the menopause it went worse. Could estrogens help?" Vaginal oestrogens (oestradiol, oestriol, conjugated estrogens, promestriene, osphemifene) can reduce the bladder vulnerability to the mechanical trauma of the intercourse.[2,23,45–48]

## Host/Woman's Vulnerabilities

Listening carefully to *women's wording* increases the ability to recognise critical *factors predisposing, precipitating and maintaining recurrences of* R-UTIs, and specifically to PCC (Table 1).

**Table1.** Recurrent post-coital cystitis: Predisposing, precipitating and maintain factors and pertinent intervention

| **Predisposing factors** | **Intervention** |
|---|---|
| Metabolic, diabetes first | Optimise the glycaemic control |
| Bladder | Exclude/treat IBCs* |
| Urethral | Protect from mechanical trauma of intercourse |
| Bacterial | Use antibiotics only in acute UTIs*- cystitis |
| Intestinal (IBS*, constipation) | Normalise bowel habits |
| Pelvic floor | Relax the pelvic floor if hyperactivity is present (with BFB* or hands-on physiotherapy) |
| Hormonal | Normalise vaginal estrogens (and vaginal pH) |
| **Precipitating factors** | **Intervention** |
| Intercourse (comorbidity with dyspareunia) | Avoid intercourse until vulvodynia is cured, the levator ani' tonus is normalised, the vaginal pH and lubrication optimised |
| Environmental (cold) | Protect the abdomen/pelvis from sudden changes of temperature |
| **Maintaining factors** | **Intervention** |
| Diagnostic omissions | Make a comprehensive evaluation |
| Inadequate treatment strategy | Address the usually unaddressed |
| Poor adherence to lifestyle and treatment plan | Share the treatment strategy with the patient to encourage her adherence to treatment |

*BFB, electromyographic biofeed-back; BCs, intracellular bacterial communities; IBS, irritable bowel syndrome; UTIs, urinary tract infections.

## Predisposing Factors

- *The metabolic factor. Insulin-treated diabetes* is a powerful predisposing factor for R-UTIs (with OR range of 2.0–3.4, across different studies).[13,14,18,41] Relapses and reinfections were reported in 7.1% and 15.9% of women with diabetes versus 2.0% and 4.1% of women without diabetes. There was an independent higher risk of R-UTIs in women with diabetes compared with women without diabetes (OR 2.0; 95% CI 1.4–2.9). Women taking oral blood glucose–lowering medication (OR 2.1; 95% CI 1.2–3.5) or insulin (OR 3.0; 95% CI 1.7–5.1) or who had had diabetes for ≥5 years (OR 2.9; 95% CI 1.9–4.4) or who had retinopathy (OR 4.1; 95% CI 1.9–9.1) were at risk of recurrent UTIs.[41] More recent researches confirm that obesity and diabetes increase the risk of R-UTIs[42] and that women with R-UTIs have a cluster of risk factors, diabetes first.[43]

- *The bladder factor*. The urothelium is coated by glycosaminoglycans (GAG's) and proteoglycans. This functional a-cellular layer, referred to as "bladder coating," is the first line of defence at the bladder's luminal surface.[23] It ensures the impermeability of the bladder surface to urine's ions and bacteria; neutralises toxic compounds; inhibits the passage of small molecules; inhibits the adhesion of UPEC and the formation of microcristals. 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 GAG layer is dynamically altered during the course of UTI. Animal data show that hormone therapy positively regulates GAG layer thickness over time, as well as the composition of the GAGs. In addition, the GAG sulfation status can be influenced by oestrogen levels in response to UPEC infection.[23]

- *The urethral factor*. The urethral mucosal, submucosal 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 the menopause.

- *The sexual factor*. Low desire, inadequate central and peripheral arousal with vaginal dryness reduce both the vaginal lubrication and the congestion of the vessels and cavernosal body around the lower third of the urethra (equivalent to part of the male corpus spongiosum), thus depriving the urethra of a vasocongestive "air-bag" against the

potential trauma of the intercourse. The traumatic potential is higher if the entrance of the vagina is reduced by the contraction of the surrounding elevator ani muscle, contributing to introital dyspareunia and PVD. In a series of 60 women with R-UTIs, Salonia *et al*.[8] recently proved that secondary PVD was reported by 36 (60%) out of the 60 patients. Women with PVD had a higher prevalence of UTIs over the last 12 months ($\chi^2$, 4.54; $p$=0.03) and more frequently suffered from UPEC-related R-UTIs ($\chi^2$, 5.92; $p$=0.01) compared to those without PVD. Moreover, women with PVD showed significantly lower scores for the *Female Sexual Function Index* domains (all $p \leq 0.01$) as compared with PVD negative individuals. UPEC-related R-UTIs (OR, 3.1; $p$=0.01), a number of UTIs ≥6 (OR, 2.8; $p$=0.01) over the last 12 months and having being treated with ≥3 antibiotics throughout the same period (OR, 2.1; $p$=0.04) emerged as independent predictors of PVD.

Sexual factors can contribute in parallel to R-UTIs and PVD, as common denominators of the tissue's traumas activating a chronic process of local inflammation, with specific characteristics according to the organ (vagina or bladder) involved.

- *The pelvic floor factor*. Pelvic floor muscles may react to tissue inflammation becoming dysfunctional and tense. The hyperactive elevator ani contributes to the mechanical trauma of the urethra when intercourse is accepted without adequate lubrication and genital congestion, and/or when fear of intercourse is prominent. Recurrent cystitis and dyspareunia since adolescence are significantly associated with bladder pain syndrome and interstitial cystitis.[5,6,48] The risk of pelvic floor dysfunction, with dyspareunia and bladder symptoms, doubles (OR=2.4) after sexual abuse.[49]

- *The hormonal factor*. Loss of oestrogens (and partially of testosterone) deprives the urogenital structures of a key trophic factor essential for a normal sexual response. The evidence on the role of oestrogens after the menopause to prevent R-UTIs is still controversial.[3,25,45–48] However, animal models of a surgical menopause support the role of oestrogens in modulating bladder health.[2,23] Ovariectomised mice had significantly higher bacteriuria, a more robust inflammatory response and increased production of the proinflammatory cytokine, IL-6, upon UPEC infection compared to sham-operated controls. UPEC-infected ovariectomised mice showed a significant increase in quiescent intracellular bacterial reservoirs (IBCs), which reside in the urothelium and can seed recurrent infections. This and other ovariectomy-induced outcomes of UTIs were reversible upon oestrogen supplementation.[2] Oestrogens maintain the *Lactobacilli*-dominated healthy vaginal ecosystem, and a low vaginal pH. Recent data suggest that in the fertile age female genital tract secretions are bactericidal for *E. coli ex vivo*. The bactericidal activity and concentration

of immune mediators in cervicovaginal lavage (CVL) reduced the number of *E. coli* colonies by 68%. CVL were active against laboratory and clinical isolates of *E. coli*, but were inactive against Lactobacillus species.[50] The role of vaginal ecosystem, oestrogen-dependent, further supports the preventing role of oestrogens in the strategy of R-UTIs prevention.

- *The vaginal pH and ecosystem*. Oestrogens are essential in maintaining the normal vaginal ecosystem, with the prominent *Lactobacilli*, which is mirrored by a vaginal pH of 4.0–4.5. A vaginal pH of 5 or more is associated with bacterial vaginosis, vaginitis and cystitis.

- *The intestinal factor*. An altered intestinal flora may lead to the overgrowth of enterobacteriaceae, the causative agents of the majority of R-UTIs, of which UPEC is the most frequently involved. 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 (barrier's violation), is a key predisposing factor to R-UTIs, frequently comorbid with IBS itself.[15,29,51] Constipation, which tends to get worse with age and menopause, is another intestinal predisposing factor.

## Precipitating Factors

- *The sexual factor*. On average 60% of R-UTI are post-coital. The risk of symptomatic UTI has a three- to four-fold increase on the second day after sexual intercourse. In multivariate analysis, frequency of sexual intercourse is the strongest risk factor for recurrence.[3] This vulnerability increases in women reporting introital dyspareunia, either lifelong[5] or acquired.[7,8,52] Figure 1 hypothesises their pathogenetic interactions. Intercourse has been shown to be the precipitating factor also in 40% of postmenopausal women.[10]

- *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 and/or bladder hypersensitivity.[53]

## Maintaining Factors

- *The diagnostic omission* of the complex pathophysiology of R-UTIs is the most important predictor of further recurrences.

- *Inadequate treatment strategies* contribute to recurrences, when predisposing, precipitating and maintaining factors are not comprehensively addressed.

- *Poor adherence* to healthy lifestyle and treatment protocol may further contribute to R-UTIs.

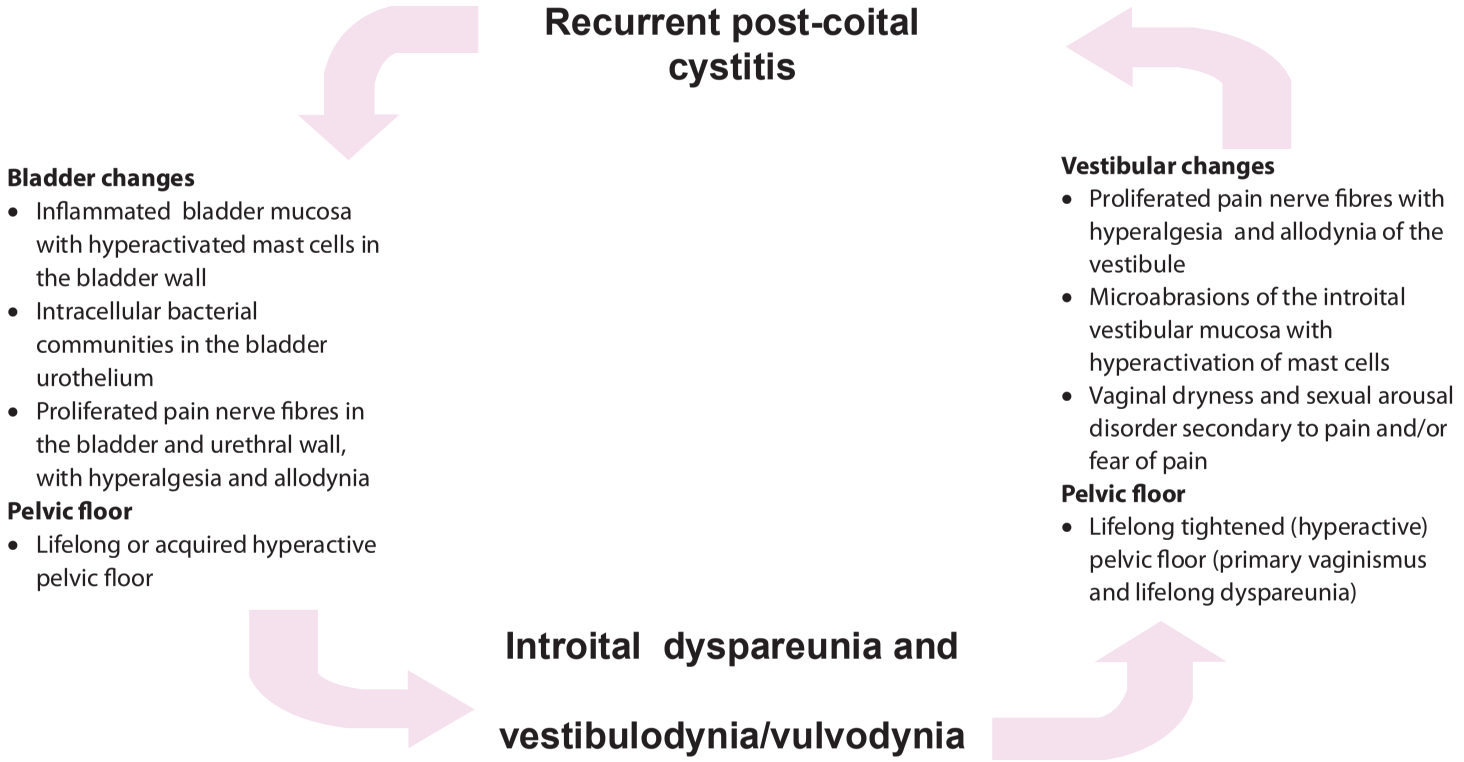


**Figure 1.** Recurrent post-coital cystitis and introital dyspareunia: a close link.

Modified from Ref. 46.

## The Identikit of the Aggressor Germs

UPEC is responsible for 85% of R-UTIs,[17,19,21,22,37,38] whereas 15% is due to *Proteus Mirabilis, Klebsiella, Enterobacter, Enterococcus fecalis, Pseudomonas aeruginosa, Staphylococcus saprophyticus, Staphylococcus aureus, Chlamydia trachomatis, Mycoplasms, Candida* spp.,[39,40] *Mycobacterium tubercolosis.* Recurrent cystitis in the fertile age are predictors of post-menopausal R-UTI (OR=6.9). The wide and repeated use of antibiotics, often on an empirical basis, is leading to antibiotic-resistance.[26] Furthermore, UPEC is also able to adopt intracellular lifestyles and immune evasion strategies, and direct a complex, intracellular cascade that shelters bacteria from host defences, thus leading to persistent bacterial residence within the epithelium, *via* the development of biofilm-like BICs.[17,19,21,22,37,38,54,55]

## Diagnosis of R-UTI: Why and When the Gynaecologist Can Help

Urologists are very competent in addressing bladder and urethral factors. However their main weapons are repeated antibiotic courses. EBM supports this choice[3,25,56] but the high risk of recurrences, antibiotic resistances and the many comorbidities – PVD/vulvodynia, dyspareunia, IBS, constipation, diabetes – challenge this germs-centred approach.

A different comprehensive approach can be more effective when based on the following:

- *Careful listening of women's wording*, rich of critical information to design a personalised protocol to prevent recurrences.
- *Mandatory questions*. Urologists usually ask question no. 1–3, whilst the others (no. 4–9) may contribute to a more accurate reading of predisposing/precipitating factors and comorbidities:

1. Is cystitis appearing 24–72 hours after intercourse?
2. Which is the pattern of recurrence: after intercourse or not?
3. Does the woman suffer from IBS, that is, diarrhoea/constipation, or obstructive constipation?
4. Does intercourse hurt at the entrance of the vagina ("introital dyspareunia")?
5. Is there a history of (recurrent) vaginal Candida infections?
6. Does the patient suffer from vulvar burning pain (spontaneous or provoked)?
7. Is she in amenorrhea (hypothalamic, postpartum, menopausal)?
8. Is she taking oral contraceptives?
9. Is she diabetic? How is her glycaemic control?

- *Mandatory gynaecological examination:*

1. *Examine the vulva and the perineum*. Is there any sign of retracted/ hyperactive pelvic floor (usually "yes" in nulliparous women reporting positive answer to question 1, 2, 4–6)? Is there any vestibular/vulvar erithema? Any discharge?

2. *Perform the swab test* (at points 5 and 7, looking at the entrance of the vagina like a clockface). Is it suggestive of comorbidity with PVD/vulvodynia and dyspareunia (present in 60% of women with PCC)? The test is usually positive when she answers yes to two out of three questions no. 4–6.

3. *Examine the pelvic floor*. Is it tense? Are there tender and/or trigger points at the insertion of the levator ani on the ischiatic spine? How's the perineal command (absent, correct, inverted, *i.e*. when the woman is requested to push and relax the levator ani/perineal floor and she automatically pulls and retract it even further)? A hyperactive pelvic floor is usually present in case of at least four positive answers to questions no 1–6.

4. *Evaluate the vaginal pH*. A pH of 4 is physiological, but associated with recurrent Candida; pH of 5 or more is associated with bacterial vaginosis and increased vulnerability to invasion/infection from colonic germs, UPEC most. Usually the vaginal pH is elevated in case of positive responses to question no 7.

- *Exams*

1. Urine analysis, cultural exam with antibiogram if acute cystitis is reported;

2. Vaginal swab for Candida, Cocchi, Ureaplasma, Mycoplasma; cervical swab for Chlamydia, when indicated;

3. Urethral swab for Ureaplasma or Chlamydia, when indicated;

4. Glycaemia, glycated Hb, glycosuria, if diabetic or with first relative affected;

5. More specific urological exams and tests should be required by the urologist, in close collaboration.

## Multimodal Strategies to Prevent Recurrences of Post-coital Cystitis

According to the available EBM (reviewed in Refs. 3, 25, 56), current therapies for R-UTIs include the following:

- Continuous antibiotic prophylaxis, lasting 6–12 months. It reduces the rate of recurrences, although there is no consensus about when to start the treatment, or about how long it should last. Trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole), nitrofurantoin, cefaclor or quinolones all seem equally effective at reducing recurrence rates. Unfortunately, they trigger quick antibiotic-

resistance in uropathogens and aggressive Candida infections, contributing to vulvar vestibulitis[7,56] and the progressive comorbidity between urologic, gynaecological and sexual symptoms. Indeed, a recent Austrian survey among general physicians indicate that the higher rates of antibiotic resistance were present with the most recommended regimens: amoxicillin/clavulanic acid (8.9), nalidixic acid (9.6), trimethoprim/sulphamethoxazole (14.4), trimethoprim (15.8), sulphamethoxazole (21.2) and ampicillin (28.8).[26]

- Post-coital antibiotics (taken within 2 hours of intercourse) reduce the rate of clinical recurrence of cystitis as effectively as continuous treatment.
- Cranberry products (either juice or capsules) seem to significantly reduce the recurrence of symptomatic cystitis. The likely mechanism is a reduction in the ability of *E. Coli* to attack the urothelial cells.[3] The last Cochrane does not support the use of cranberry in preventing R-UTIs,[56,57] although it can be used as a complementary therapy.
- Passing urine after the intercourse. There is no evidence examining whether it is effective at preventing UTI.

Unfortunately, the above-mentioned approaches tend to attack/eliminate the germs *after* they reached the bladder. A different strategy is presented here aiming at reducing predisposing, precipitating and maintaining factors (Table 1, column of intervention strategy).

Key interventions, where the gynaecologist can really make a difference in the prevention of R-UTI/PCC, include the following:

- Topical oestrogens, to be considered when clinically indicated (non-pregnancy related amenorrhoea for more than 3 months, or when the vaginal pH is equal or above 5). Animal data[2,23] and pathophysiological studies[50] support a specific protective role.
- Reduce premenstrual flares of bladder vulnerability and pain, by using a continuous pill. This approach reduces/eliminates oestrogen's fluctuations, the associated increase in mast-cell's degranulation and the premenstrual worsening of symptoms associated with R-UTIs.
- Normalise the tonus of the pelvic floor, with electromyographic biofeedback (BFB) (specifically indicated in case of an inverted command of the pelvic floor), and/or hands-on physiotherapy.[5–7,58,59] This intervention should be mandatory in case of comorbidity with introital dyspareunia/PVD/vulvodynia. Normalising the pelvic floor reduces/eliminates the mechanical component of the bladder damage, which increases the vulnerability to bacterial attacks after intercourse.

- Cure comorbidity with vulvar vestibulitis/PVD, as pain maintains and worsens the defensive contraction of the pelvic floor.[7,60]
- Prevent and cure candida recurrences, cofactors in vulvar vestibulitis/vulvodynia.[7]
- Normalise bowel habits and/or refer to a competent gastroenterologist to address IBS. Probiotics can contribute to improve the colonic ecosystem, devastated by recurrent/prolonged antibiotic courses.[29,61]
- Recommend optimal glycaemic control and a low glucose diet in women vulnerable to recurrent Candida.
- A close collaboration with the urologist, and the reciprocal learning, is the core of this more comprehensive intervention.

## Conclusion

R-UTIs, and specifically PCCs, are becoming a clinical challenge, increasingly relevant in terms of women's suffering, couple problems and social costs: quantifiable, in terms of out-patients visits, exams, antibiotics, loss of work-days and non-quantifiable, in terms of distress, suffering, sexual and relational problems.[62,63] Listening to women's wording, asking proper questions, carefully examining the vulva, the pelvic floor, the vagina, will increase the diagnostic accuracy, the appropriate reading of comorbidities and the design of a personalised treatment protocol. The gynaecologist may help women in preventing R-UTIs, by diagnosing and addressing the many factors he/she is familiar with by training that are not usually considered in the urological approach. A close collaboration between urologists and gynaecologist is helpful in reducing R-UTIs in women. Controlled studies using this collaborative approach are necessary to confirm its validity.

## Key Points

- "Cystitis" indicates the presence of infections and/or inflammation of the bladder and urethra, accompanied by urinary symptoms. It causes both pain when passing urine, urgency and, sometimes, haematuria; suprapubic pain not associated with passing urine.
- In women, cystitis is the most frequent clinical presentation of UTIs; 50–60% of women have at least one episode of cystitis after puberty. First episodes frequently coincide with the beginning of sexual intercourse. Comorbidity with introital dyspareunia and PVD (former vulvar vestibulitis) is present in 50–60% of women.
- R-UTIs is defined as three or more episodes in 12 months or two or more episodes in 6 months. UPEC is the most frequent etiological bacteria. Cystitis after intercourse (PCC) accounts for 60% of recurrent cystitis. In the adulthood, recurrent cystitis is reported in 1 woman out

of 3, and 1 man out of 20.

- Pathophysiology of R-UTIs is complex. Prevention of recurrences requires intercepting and curing:

    1. Predisposing factors – hyperactive pelvic floor; sexual dysfunctions (inadequate genital arousal with vaginal dryness); loss of oestrogen with high vaginal pH; altered vaginal ecosystem; lesion of the "bladder coating" made of GAGs and proteoglycans; inadequate "sealing" effect of the urethra; IBS, obstructive constipation, altered intestinal ecosystem; diabetes with poor glycaemic control.

    2. Precipitating factors – intercourse with poor/absent lubrication and/or a tighten pelvic floor, causing PCC; sudden environmental cold ("a frigore").

    3. Maintaining factors – diagnostic omissions, inadequate treatment strategies, poor adherence to healthy lifestyle and treatment protocol.

- *Women's wording* is key. Then *questions* should inquire timing of the PCC, pattern of recurrence, comorbidity with pain at the beginning of penetration ("introital dyspareunia"), Candida infections, vestibular pain, IBS, obstructive constipation, diabetes.

- Physical examination should include careful examination of the vulva and vestibule, looking for erythema; swab test for tenderness and elicit pain/burning at 5 and 7 of the introitus; evaluation of the pelvic floor in static and dynamic conditions; recording of the vaginal pH.

- Exams include urine analysis and cultural exams; cervical, vaginal and urethral swabs, glycaemia and glycated Hb and other specific exams when indicated.

- *Therapy*. Cochrane reviews recommend continuous antibiotic prophylaxis up to 6–12 months, post-coital antibiotics; cranberry products as complementary – measures all focused on attacking germs to prevent/reduce infections at the price of complex antibiotic resistances and devastation of intestinal and vaginal ecosystem.

- This paper suggests the importance of *improving the host/woman resistances* to infection – normalise the hyperactive pelvic floor, with physiotherapy and/or electromyographic biofeed-back; cure comorbidity with sexual factors, contributing to UTIs, vaginal dryness, introital dyspareunia, PVD and Candida infections; normalise bowel habits; recommend optimal glycaemic control and proper diet; use vaginal oestrogens (when non contraindicated) when pH is above 5 and specifically after the menopause.

**Box 3.** Where do germs causing cystitis come from?

From the colon:

- via the "endogenous" pathway, through the "barrier's violation." This wording indicates the passage of germs from the intestinal ecosystem, through the colonic wall, inside the blood and then to the bladder wall and/or the vagina. The colonic "barrier" competence against germs and food allergens is impaired by the chronic inflammations associated with IBS (with alternating diarrhoea and constipation). The results are recurrent cystitis and vaginitis from Enterobacteriacee, that is, colonic germs.
- via the "exogenous" pathway – germs may get backward to the bladder through the urethra, if the external genitalia are contaminated with faeces, due to inappropriate hygiene or to the sexual habit of having anal play/intercourse and then the vaginal one, without proper washing.

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