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Review

# Estrogenic action on innate defense mechanisms in the urinary tract

Petra Lüthje[a], Angelica Lindén Hirschberg[b], Annelie Brauner[a,*]

[a] Department of Microbiology, Tumor and Cell Biology, Division of Clinical Microbiology, Karolinska Institutet and Karolinska University Hospital, 17176 Stockholm, Sweden
[b] Department of Women's and Children's Health, Division of Obstetrics and Gynecology, Karolinska University Hospital and Karolinska Institutet, 17177 Stockholm, Sweden

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ABSTRACT

Clinical data suggest an impact of estrogen on the pathogenesis of urinary tract infections (UTI). In particular, women after menopause often suffer from recurrent UTI, characterized by at least three acute UTI episodes within a year. Aside from bacterial factors promoting persistence within the urinary bladder, the low estrogen levels induce structural and chemical changes in the urogenital tract which facilitate UTI. Increased residual urine volume and changes in the vaginal microflora are well documented risk factors. Local supplementation with estrogen can at least partly reverse these changes. Treatment allows the re-establishment of a lactobacilli-dominated vaginal microflora and improves epithelial differentiation and integrity in the urogenital tract. This estrogenic effect on the epithelium is marked by an increased production of antimicrobial peptides and a tighter intercellular connection, preventing bacteria from reaching cells where they can hide and later emerge and cause a new infection. Estrogen in the dosages and applications used to date is considered safe for the endometrium in the majority of women. Based on the actions and safety of estrogen, local supplementation thus offers a treatment option for postmenopausal women suffering from recurrent UTI.



**Contents**



* Corresponding author at: Division of Clinical Microbiology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden. Tel.: +46 8 5177 0000; fax: +46 8 308099.
*E-mail address:* Annelie.Brauner@ki.se (A. Brauner).

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## 1. Introduction

Infections of the urinary tract belong to the most common infectious diseases worldwide and are a major economic burden for the public health care system [1]. Remarkably, urinary tract infections (UTI)[1] affect mainly women. About 50% of women experience at least one UTI during their lifetime, and more than 25% of these initial infections recur. Besides the close proximity of the female urethra to the vagina and anus, an impact of estrogen on UTI pathogenesis is generally accepted, although the underlying mechanisms are still incompletely understood. While estrogen appears to be a risk factor for infection in young women [2], the same hormone also supports defense mechanisms to eradicate bacteria from the urinary tract [3]. This is mirrored by the increased risk to develop recurrent infections after menopause when estrogen levels are low.

Estrogen, in addition to its well-known effect on growth and differentiation of the female reproductive system, acts also on non-reproductive tissues. The activity is exhibited *via* two types of estrogen receptors (ER), ERα and ERβ, with differential tissue expression patterns and functions. In the urinary bladder, ERβ is the major ER type [4] and is involved in epithelial differentiation and maintenance [5,6], whereas ERα is dominating in the vagina.

This review intends to summarize well acknowledged risk factors for UTI related to the hypoestrogenic condition after menopause; and to give an overview about clinically or experimentally confirmed mechanisms, by which exogenous estrogen may improve the situation for postmenopausal women suffering from recurrent infections.

## 2. Bacterial persistence in the urinary tract

Uncomplicated UTI are primarily caused by uropathogenic *Escherichia coli* (UPEC) [1]. This group of extraintestinal *E. coli* is defined based solely on its association to an infection of the urinary tract. UPEC present in fact a highly heterogeneous group of strains adapted to survive in the urinary tract [7].

With increasing resistance to conventional antimicrobial agents, alternative treatment strategies are highly needed. To boost the endogenous immune defense appears an attractive option [3,8], with a low risk for bacteria to develop resistances. Although antimicrobial therapy selects for resistant bacteria, the ability to persist is not necessarily associated with antimicrobial resistance. UPEC has for a long time been considered an extracellular pathogen, but now it is well recognized that these bacteria invade and persist inside epithelial cells, a niche protected from antibiotics as well as host defense mechanisms. Thus, bacterial factors enabling *E. coli* to invade the host cell and to persist intracellularly are highly relevant for persistent infections to occur. A number of studies have demonstrated the association of certain virulence factors for *E. coli* to persist in the host. Virulence factors mediating adhesion, biofilm formation or involved in iron acquisition appear of particular importance [7,9–11].

## 3. Risk factors for UTI after menopause

After menopause, declining levels of estrogen induce a condition referred to as vulvovaginal atrophy in 25–50% of women [12]. Symptoms include vaginal dryness, itching and a rise in vaginal pH as well as urinary frequency and incontinence. These changes impair also the defense against invading pathogens and thus may contribute to the increased risk for UTI after menopause. The prevalence rate of UTI is 8–10% in postmenopausal women, and 5% of these women will have a recurrent infection within one year [13].

### 3.1. The urinary bladder

Incomplete emptying of the urinary bladder, expressed by the volume of residual urine after voiding is one factor amongst those suggested to increase the risk of recurrent UTIs after menopause. The association between low estrogen and high residual urine is well established [14,15]. Studies on rabbit bladders demonstrate that estrogen increases the volume of smooth muscle cells and vascularization in the bladder body, while decreasing collagen, resulting in higher contractility of the bladder [16]. Residual urine and a reduction in urine flow in the absence of estrogen [15], impairs the mechanical clearance of bacteria from the bladder and facilitates pathogens to colonize the tissue and to establish an infection.

### 3.2. The vaginal microflora

The microflora in healthy menstruating women is dominated by lactobacilli. They produce lactic acid, hydrogen peroxide and bactericidal proteins, which restrict the growth of pathogenic bacteria such as *E. coli* [17]. This normal microflora thus confers protection against invading pathogens, while an abnormal colonization is associated with UTI [18].

Estrogen promotes lactobacilli growth by increasing the storage of glycogen in the cells of the vaginal epithelium [19], the substrate for acid production by these bacteria. With declining glycogen availability the number of lactobacilli declines and the vaginal pH rises. In postmenopausal women a multispecies microflora linked to a higher vaginal pH is therefore more likely to occur [20,21], facilitating the growth of potential pathogens. It has also been proposed that estrogen regulates the vaginal pH by acting on the epithelial cells directly [22]. However, most studies support the hypothesis that a low vaginal pH depends on the presence of acid-generating bacteria [23].

## 4. Effect of estrogen supplementation

### 4.1. Clinical studies

The results from clinical studies about the effect of estrogen supplementation after menopause on recurrent UTI are divergent [13]. While two placebo-controlled studies demonstrate that locally applied estrogen reduces recurrence [24,25], studies using oral supplementation overall do not show significant improvements compared to placebo [13]. The low efficiency of oral supplementation is supported by studies, which were not restricted to cases of recurrent UTI. However, in one study involving postmenopausal women suffering from urinary symptoms including UTI [26], local estrogen treatment was strongly associated to low UTI frequencies, while this linkage was only weak for systemic treatment.

In a group of postmenopausal women with or without UTI, oral hormone replacement therapy was associated with a lower residual urine volume, which in turn was associated to a lower risk of UTI [14]. Functional studies in postmenopausal women are spars and cannot prove significant effects [27], but improvement of bladder functions by estrogen has been demonstrated in animals [16].

### 4.2. The vaginal mucosa

It is well established that estrogen supplementation provides relief from vaginal symptoms associated with postmenopausal

[1] CAMP, cathelicidin antimicrobial peptide; ER, estrogen receptor; hBD, human β-defensin; NGF, nerve growth factor; RNase, ribonuclease; UPEC, uropathogenic *Escherichia coli*; UTI, urinary tract infection; VEGF, vascular endothelial growth factor.