Immunostimulation with *Escherichia coli* extract: prevention of recurrent urinary tract infections

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**Abstract**

Antibiotic treatment is the most effective method for managing recurrent uncomplicated urinary tract infections (UTIs) in women. However, there is a limitation to long-term antibiotic use, therefore alternative approaches are required. *Escherichia coli* is the commonest cause of recurrent uncomplicated UTIs and accounts for more than 60% of recurrent cystitis. It has therefore been suggested that immunostimulation with a bacterial extract consisting of immunostimulating components derived from 18 *E. coli* strains may protect against UTIs. Many in vitro studies, animal experiments and clinical trials in patients with recurrent UTIs have been carried out to assess the effectiveness and safety of *E. coli* extract for prophylaxis against recurrent UTIs. In this paper, we review the scientific evidence showing the anti-inflammatory effect of *E. coli* extract as well as the clinical results of placebo-controlled, randomised, double-blind studies that demonstrated a positive effect for *E. coli* extract in patients with recurrent UTIs. Evidence from available studies suggests that *E. coli* extract can be beneficial and safe for preventing recurrent UTIs in women.

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**1. Introduction**

Urinary tract infections (UTIs) are common in medical practice and range from asymptomatic bacteriuria to debilitating acute pyelonephritis. UTIs are especially problematic for women; 50–80% of women will suffer at least one episode of UTI in their lifetime and 20–50% of women will have recurrent episodes [1,2]. Recurrent UTIs secondary to re-infection are more common than relapse or persistent infections and account for 80% of recurrent UTIs. The majority of these infections are uncomplicated, that is they occur in women with no anatomical or other apparent predisposing reason for infection, such as recent instrumentation, gynaecological or urological surgery, or pregnancy.

In a study of college women with their first UTI, 27% experienced at least one culture-confirmed recurrence of infection within the 6 months following the initial infection [3]. In a Finnish study of women aged 17–82 years who had *Escherichia coli* cystitis, 44% had a recurrence within 1 year, 53% in women older than 55 years and 36% in younger women [2]. Although epidemiological data for older women are sparse, it is estimated that 10–15% of women over the age of 60 years have frequent recurrences [4].

Most uropathogens causing recurrent UTIs originate in the gastrointestinal tract and enter the bladder via the urethra [5]. *Escherichia coli* is the most frequent cause of cystitis and is responsible not only for 85% of asymptomatic bacteriuria and acute cystitis but also accounts for more than 60% of recurrent cystitis [6]. According to a clinical study, the incidence of bacterial cystitis caused by *E. coli* was 0.39–0.53 episodes per person-year among women aged 18–40 years [7].

Infection should be treated with a full course of an appropriate antibiotic. Thereafter, there are several approaches...
available that can be employed to prevent recurrences, such as long-term, low-dose antibiotic prophylaxis, post-coital antibiotics and self-start therapy, which have all been demonstrated to be effective in managing recurrent uncomplicated UTIs in women [5]. However, in view of the emergence of antibiotic resistance and attenuation of the host response, there is limitation in long-term antibiotic use [8,9]. Alternative approaches are therefore necessary. Oral administration of an immunostimulating agent that prevents recurrent UTIs without the undesired effects of long-term antibiotic use is very attractive.

This review describes an oral immunostimulating agent (an *E. coli* extract) as an alternative approach to the prevention of recurrent UTIs.

2. What is *E. coli* extract?

Uro-Vaxom® (OM Pharma, Geneva, Switzerland) is a purified *E. coli* extract that is administered orally. It is composed of immunostimulating components derived from 18 different strains of *E. coli* antigens. The extract of 18 strains of *E. coli* is obtained by alkaline lysis, which destroys lipopolysaccharide (LPS) molecules and modifies bacterial antigens, maintaining their antigenic potential even after oral administration. Immunostimulation occurs via intestinal Peyer’s patches, the intestinal organ playing an essential role in stimulation of the immune system.

The product is presented as capsules and has been registered and sold in Switzerland since 1988 and in Germany since 1989, and has been successfully marketed for several years in several Eastern European countries (Poland, Czech Republic, Slovakian Republic, Hungary and Slovenia).

The *E. coli* extract stimulates many host defence mechanisms to bring about its immunostimulating effects. In in vitro studies, researchers found that this agent could promote the production of interleukin (IL)-2 [10], IL-6 [10], tumour necrosis factor-alpha (TNF-α) [10] and interferon-gamma (IFN-γ) [10] from monocytes in the peripheral blood. It also promoted macrophage phagocytosis [12] as well as the activities of natural killer cells and the polyclonal B-lymphocyte activator [13,14].

Recent studies have demonstrated immunostimulation with Uro-Vaxom, particularly the production of antibodies to *E. coli*. Sedelmeier and Bessler [15] found that multiple oral administration of *E. coli* extract led to the production of *E. coli* extract-specific antiserum. These antibodies were mainly immunoglobulin (IgG); a weak increase of IgM and high-level antibodies was obtained following long-term oral administration. This study demonstrated that *E. coli* extract could act as a specific immunogen in mice.

Subsequently, Huber et al. [16] investigated the immunogenicity of *E. coli* extract following intraperitoneal or oral administration in a mouse model. This study demonstrated three important findings that explained the mechanism of prevention of recurrent UTIs. First, antiserum obtained following repeated administration was able to recognise the 18 *E. coli* strains used for preparation of the *E. coli* extract. This antiserum also recognised a variety of other human pathogenic bacterial strains isolated from patients with UTIs (*Enterococcus faecalis*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis* and *Proteus rettgeri*) [16]. Second, the study found an increased level both of bacterial strain-specific and of total IgG and IgA when investigating antibody production in cell culture supernatants of the urogenital tract of *E. coli* extract-treated animals [16]. Third, the increase in bacteria-specific serum IgA levels demonstrated in this study indicated that a mucosal immune response was also initiated following the administration of the bacterial extract. Through stimulation of the mucosal immune system, B-cells of the urogenital tract increase the production and secretion of strain-specific and total IgG and IgA. Fig. 1 summarises
the mechanism of action and effects of *E. coli* extract on the immune system, which are presumably based on previous in vitro and in vivo studies.

The anti-inflammatory effect of *E. coli* extract was evaluated by measuring the cytokine levels in bladder tissue following oral administration in a model of LPS-induced cystitis in mice [17]. Bladder inflammation was studied by histopathological examination. In this study, administration by mouth of the *E. coli* extract significantly inhibited the cystitis induced by *E. coli* LPS, where all the inflammatory indices including bladder oedema, leukocyte infiltration and haemorrhage indices were lower in the study group than in the control group. The levels of IL-6 and IFN-γ measured in bladder tissue following *E. coli* extract were significantly increased [17]. The anti-inflammatory effects of *E. coli* extract can be attributed to the immunostimulating effects of IL-6 and IFN-γ, as found in previous studies that reported the immunostimulating effects of the *E. coli* extract [10–18]. These data enable us to postulate that the higher levels of pro-inflammatory cytokines, such as IL-6 and IFN-γ, can play a role in making the host response stronger.

The above-mentioned in vitro and in vivo studies [10–18] provided us with a scientific basis to initiate clinical studies with the intention of preventing recurrent UTIs.

3. **Clinical studies of the *E. coli* extract**

Several studies on the efficacy of *E. coli* extract for the prevention of recurrent UTIs have been performed since the first clinical study was done by Frey et al. in 1986 [19]. In the first report, 64 outpatients, mostly women suffering from recurrent lower UTIs, were treated with one capsule daily for 3 months followed by a 3-month observation period. This study reported that dysuria, bacteriuria, leukocyturia and antibiotic consumption showed a significant reduction in the *E. coli* extract-treated patients compared with the placebo group. The criteria used to assess the treatment outcome were principally the rate of UTI recurrence (number of recurrences), the consumption of antibiotics and the incidence of bacteriuria, leukocyturia and dysuria. The rate of recurrence of UTIs is the most important factor in clinical practice. After Frey’s report, the number of recurrences of UTI has been the primary endpoint in reports.

There are three clinical studies that are double-blind, randomised and placebo-controlled with similar protocols (3-month duration, same dose treatment, with observation and a further observation period of 3 months without treatment) [20–22]. All of these studies showed that a 3-month course of *E. coli* extract treatment significantly reduced the number of recurrences during a 6-month period, although the recurrence rate varied in different studies (Table 1).

Tammen [20] described 120 patients with recurrent UTIs who had approximately 3.5 recurrences of infection during the 6 months preceding the trial. In the trial, the mean number of recurrences in the treatment group was 0.82 (50/61) and 1.8 (104/59) in the placebo group. The total number of recurrences was significantly lower in the *E. coli* extract treatment group than in the placebo group, being 38 and 63 ($P<0.05$), respectively, during 3 months treatment and 12 and 41 ($P<0.01$) during the subsequent 3 months following treatment.

In another trial using a similar protocol, recurrence was defined as bacteriuria > $10^4$ bacteria/mL or bacteriuria > $10^5$ bacteria/mL, and clinical evaluation was performed according to each definition. The mean number of recurrences with bacteriuria of at least $10^5$ bacteria/mL for the total study duration was 0.7 in the *E. coli* extract treatment and 1.5 in the placebo group, and for recurrence with bacteriuria of at least $10^4$ bacteria/mL it was 1.2 compared with 2.0 [21].

Magasi et al. [22] also demonstrated a significant effect of *E. coli* extract for the prevention of recurrent UTIs. During the entire period of the trial, the frequency of recurrence was 8 (13.8%) of the total cases in the *E. coli* extract group compared with 43 (79.6%) in the placebo group ($P<0.0005$).

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$^a$ $n_1/n_2$, results expressed as the number of positive findings ($n_1$) with respect to the total number of cases ($n_2$).

A meta-analysis was performed on the above four clinical studies [19–22] carried out to demonstrate a positive effect for E. coli extract and to give an overview of the previous five studies [18]. In all five studies (601 women suffering from recurrent UTIs), the E. coli extract group was statistically superior to the control group with respect to reduction in the frequency of UTIs and also to dysuria, bacteriuria and leukocyturia.

With regard to antibiotic consumption, there was a distinct difference between the two groups [20,21]. Schulman et al. [21] reported that antibiotic consumption had decreased significantly during the 3 months of treatment with E. coli extract but had remained practically the same in the placebo group.

To date, a course of antibiotic treatment has been the most effective prophylaxis for the prevention of recurrent UTI. However, cessation of antibiotic treatment usually results in recurrence of infection in most patients [1]. The finding that the inhibitory effect of E. coli extract lasts for more than 3 months after the drug has been discontinued suggests indirectly that changes in the immune system can affect the development of UTIs.

In the above-mentioned clinical trials, the efficacy of E. coli extract has been shown for up to 6 months, i.e. 3 months treatment followed by a 3-month observation period without treatment. Bauer et al. [23] performed a study to investigate further long-term preventive effects of the extract in uncomplicated recurrent UTIs. It was the largest study to date, in which a total of 454 female patients were enrolled and booster courses were added to the protocol of previous clinical trials. Patients received E. coli extract or placebo during the first 3 months followed by another 3 months without treatment. Then booster doses for 10 days were given during months 7–9 and patients were followed-up for 12 months without treatment. The rate of recurrence was significantly lower in the vaccine group, in which recurrences were reduced by 34% compared with the placebo group (Table 1). In the vaccine group, 93 patients (40.3%) had 185 recurrences of infection compared with 276 recurrences in 122 patients (55.0%) in the placebo group. The positive results of the booster doses suggest the possibility of repeated treatment in the following year. This study, which gave 3 months of treatment and then three 10-day booster courses, appeared to be effective in prevention of recurrent UTIs for 12 months [23].

The safety profile of E. coli extract has been determined in clinical studies [19–23]. Most patients treated with E. coli extract experienced minor adverse events as frequently as patients in the placebo group. The most frequent adverse events were headache and gastrointestinal side effects, but there were no safety concerns with regard to laboratory variables and clinical signs. There were no reports of serious or unexpected treatment-emergent adverse events in the clinical studies. The E. coli extract had good tolerance and excellent compliance throughout the studies.

4. Conclusion

There has been an increasing requirement for alternative approaches to antibiotic prophylaxis for preventing recurrent UTIs. Oral administration of the immunostimulating agent E. coli extract is considered an alternative approach for the prevention of recurrent UTIs in women.

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References


