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IMMUNOSTIMULATING AND PROPHYLACTIC EFFECT OF E. COLI EXTRACT IN A MOUSE MODEL OF LIPOPOLYSACCHARIDE-INDUCED CYSTITIS

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INTRODUCTION & OBJECTIVES: A bacterial extract (Uro-Vaxom®) consisting of immunostimulating components derived from 18 *Escherichia coli* strains has been used for the prophylaxis of recurrent cystitis. To evaluate the prophylactic effect of *E. coli* extract, we measured the cytokine levels of bladder tissue after oral administration and analyzed bladder inflammation by histopathologic examination in a model of lipopolysaccharide (LPS)-induced cystitis in mice.

MATERIAL & METHODS: After 10-day administration of *E. coli* extract, cytokine [interleukin-6 (IL-6), IL-10, monocyte chemoattractant protein-1 (MCP-1), interferon-γ (IFN-γ), Tumour necrosis factor-α (TNF-α), IL-12p70] levels in the bladder of female Blab/C mice were determined using cytometric bead array. Bladder macrophage inflammatory protein-2 (MIP-2) level was also measured using sandwich enzyme immunoassay. After immunization with *E. coli* extract, *E. coli* LPS was instilled into the bladders. Twenty-four hours later, mice were sacrificed and inflammations of the bladder were quantified using the bladder inflammatory index (BII).

RESULTS: Significant increases of IL-6 and IFN-γ in bladder tissue were observed after *E. coli* extract treatment. Secretions of other cytokines were not stimulated by *E. coli* extract. Bladder instilled with LPS showed high inflammation scores for edema, leukocyte infiltration, and hemorrhage in saline treated control mice. In contrast, *E. coli* extract treated mice exhibited mild inflammation of their bladders with significant reduction of BII scores compared to controls.

CONCLUSIONS: These results demonstrate that immunization using oral treatment of *E. coli* extract provides protection of inflammatory responses in a mouse model of LPS-induced cystitis.

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EFFECTIVENESS OF URO-VAXOM AND VITAMIN E IN DELAYING RECURRENCES OF E.COLI LUTS IN GERIATRIC PATIENTS

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INTRODUCTION & OBJECTIVES: Uro-Vaxom is an oral vaccine against Escherichia coli used as immunobiotherapy of urinary tract infections. Vitamin supplementation is thought to improve immunity and thereby reduce infectious morbidity in elderly patients. Aim of this study was to investigate the effects of Uro-Vaxom in a combination treatment with vit. E in delaying recurrences of lower urinary tract infections in geriatrics patients.

MATERIAL & METHODS: A total of 60 institutionalized elderly patients aged 75 to 90 (m.a.78.5) with recurrent lower urinary tract infection (LUTS) concluded the 6-month period of the double-blind, placebo-controlled study. Patients were treated for 4 months. The follow-up period was continued for two more months. Patients were treated either with placebo (30 patients), or with one capsule daily of Uro-Vaxom (UV) and 100mg vit. E twice daily (30 patients). All patients received additionally an antibiotic or chemotherapeutic in low regimen dose. We evaluated parameters such as treatment tolerance, number of recurrences, the incidence of bacteriuria, dysuria, haematuria and leukocyturia as well as the adverse reactions of this treatment.

RESULTS: During the 6 months of the trial a considerable reduce in the number of recurrences ($p < 0.0005$) was noted in the UV plus Vit.E group as compared to the placebo group. Only six cases of E.coli LUTS were registered (20%) whereas 12 cases of re-infection (40%) were registered in the placebo group. The incidence of bacteriuria (germs $\geq 10^5$/ml), dysuria and leukocyturia was significantly reduced in the first trial arm. UV and Vit. E was well tolerated and no side effects were recorded during the trial.

CONCLUSIONS: Oral immunotherapy with the Uro-Vaxom Escherichia coli extract with supplementation with antioxidant agents like vitamin - E, can reduce the incidence of recurrent urogenital infections and reinforce some of the immune dysfunction associated with advanced age.

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BACTERIAL SPECTRUM AND ANTIBIOTIC RESISTANCE OF UROPATHOGENS IN HOSPITALIZED UROLOGICAL PATIENTS WITH URINARY TRACT INFECTIONS (1994-2004) AND CONSEQUENCES FOR THE EMPIRIC ANTIBIOTIC THERAPY

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INTRODUCTION & OBJECTIVES: Surveillance of the bacterial spectrum and antibiotic resistance of uropathogens is important for the right antibiotic choice. Uropathogens causing complicated urinary tract infections (UTI) in the years 1994-2004 were tested.

MATERIAL & METHODS: In the years 1994 -2004 all uropathogens of hospitalized urological patients were identified and the susceptibility was tested against 14 antibiotic substances (trimethoprim (TMP)/sulfamethoxazole (SMZ), ciprofloxacin, ampicillin, mezlocillin, ampicillin/ sulbactam, piperacillin/ tazobactam, cefuroxime, cefpodoxime, cefotaxime, ceftazidime, gentamicin, penicillin, oxacillin and vancomycin). Since 2002 levofloxacin, gatifloxacin, piperacillin/ sulbactam and linezolid were tested additionally. For the statistical evaluation duplicate isolates were eliminated.

RESULTS: 1. There was no general trend in the emergence of resistance, except with TMP/SMZ and ciprofloxacin in *E. coli*. 2. Vancomycin or linezolid intermediate or resistant staphylococci or enterococci were not observed. 3. The lowest rate of resistance was observed with piperacillin / tazobactam; carbapenems however were not tested regularly.

CONCLUSIONS: If the uropathogens are stratified into Gram positive and negative bacteria, for oral application ciprofloxacin or levofloxacin showed the lowest resistant rates for Gram negative, ampicillin/ sulbactam, gatifloxacin or linezolid for Gram positive uropathogens. After further differentiation of uropathogens with quick and simple methods, i.e. catalase, koagulase, oxidase testing, the empiric antibiotic therapy can be done more taylored. In order to be able to do so, the urologist has to become involved in the analytic processing of the urine probe.

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ULTRASTRUCTURAL CHANGES WITHIN THE URINARY BLADDER FOLLOWING RECURRENT URINARY TRACT INFECTION

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INTRODUCTION & OBJECTIVES: Recent studies into the interaction of uropathogenic Escherichia coli (UPEC) and the urinary bladder epithelium have produced a new hypothesis that may explain the recurrent nature of UTI. It has been shown that UPEC not only attach to the surface of the luminal cells but also internalise and multiply to form intracellular bacterial colonies. To avoid excretion, the intracellular bacteria change their morphology to form long thread like structures, aiding their penetration into adjacent uninfected cells. Thus the UPEC form a reservoir for infection to recur. This hypothesis has been shown on a mouse experimental model in acute phase of infection. We have investigated whether similar changes could be seen in patients with recurrent UTI.

MATERIAL & METHODS: We recruited six patients with proven recurrent UTIs and four healthy adults (age 19 - 35 years) as controls. Each volunteer underwent a flexible cystoscopy under local anaesthetic and 3 biopsies were taken. One of the 3 samples was used for light microscopy, one sent for transmission electron microscopy (TEM) and the last sample was snap frozen for future use.
To understand the changes in the bladder in acute infection, we developed an experimental mouse model with acute UTI by directly inoculating 10^8/ml UPEC into the bladder. The mice were sacrificed at 24 hours, 7 days and 15 days post infection and bladders were dissected. The bladder was sent for scanning electron microscopy, TEM and light microscopic (LM) analysis.

RESULTS: LM showed increased no. of inflammatory cells including lymphocytes plasma cells and mast cells but no polymorphonuclear cells were seen. There was no evidence of intracellular UPEC in the infection group.
TEM showed large number of secondary lysosomes within the urothelial cells. The mean number of secondary lysosomes was significantly higher (Infection gp mean =5.284; Control gp mean =2.603 p = 0.0445) in infection group. The other changes included duplication and thickening of the basement membrane. However, no intracellular bacteria were observed in any of the samples.
In the mouse model, though the UPEC internalise into the epithelial cells and change morphology to long fluxing bacteria, it was only seen in the first 24 hours. In the following time periods the changes within the cell were similar to those seen in the human bladders with recurrent infection i.e. there were increased number of secondary lysosomes.

CONCLUSIONS: Bacteria have been shown to invade and internalise into bladder cells in acute UTI in animal models. We were unable to identify intracellular bacteria in patients with recurrent UTI. However, light microscopic and ultra structural changes seen in these patients suggest possible ongoing biochemical and immunological changes within the epithelium even in the absence of UTI. The natures of these changes are the subject of ongoing studies.