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ORIGINAL ARTICLE

Immunotherapy with an oral bacterial extract for urinary tract infections

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Background. This study has made to demonstrate efficacy and safety of oral bacterial extracts in reducing the number of urinary tract infection episodes.

Patients and methods. in 20 patients (group A), we gave 1 capsule per day of bacterial extract during 3 months with their conventional antibiotics. All the patients having had more than 2 urinary tract infections during the last 6 months and having actually an acute infection with dysuria, fever and bacteruria. In 10 patients (group B) with the same criteria we did not gave bacterial extract but only antibiotics and we used them as the control group. The duration of the study was 9 months. Women were 60%, chronic renal failure and nephrolithiasis persisted in 20%. Gram(-) bacteria revealed in 80%.

Results. The first 3 months 54% of the patients from group A had none recurrence. After 6 months from the end of receiving bacterial extract in group A:37% had 1 episode and 67% in the control group ($p<0,05$). The intensity and duration of symptoms were diminished in A group in comparison with the control group. Adverse reactions like diarrhoea and headache revealed in 4% not so serious to discontinue the medicine. All the patients finished this protocol.

We conclude that the purified bacterial extracts diminish the intensity and the recurrences of urinary tract infections. They seem to be safe and effective without serious sides effects.

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Lower urinary tract infections are very common infections in the adult population for the nephrologists and urologists. Women represent 80-90% of these patients. 10-20% of the women will have at least one infection episode during their adult life[1,2]. After the initial episode 30% of this population will have at least one recurrence the next 6-12 months. The incidence of recurrences is higher 2 months after the first episode and diminishes thereafter[3,4]. Patients with uncomplicated lower or upper urinary tract infections respond quite well in antibiotics , with full remission in their symptoms. However the overuse of antibiotics has led to the development of resistance. In addition to their relatively high costs and side effects, antibiotics often provide a palliative treatment which is effective against acute infections. In general, antibiotics are powerless to prevent the disease from recurring or from becoming chronic. The recent years patients and doctors have the responsibility to use antibiotics rightly and prudentially[5].

The different serotypes of escherichia-coli are the most common pathogens for lower urinary tract infections , especially responsible for 80-90% of the community infections[6]. In some patients suggest the longterm use of low doses of antibiotics to prevent the infection recurrences. This group include women with more than 2 infection episodes during 6 months, men with chronic prostatitis and asymptomatic pregnant women with bacteruria[7].

As we mentioned the huge use of antibiotics is related with the appearance of resistant bacteria so the alternative strategies are very important. The use of immune-stimulators is a real good option. Ingestion of bacterial products stimulates the responses of different immune cells , resulting in particular in a higher production of secretory IgA at distal mucosal sites[8,9]. Under certain conditions a state of nonreactivity or oral tolerance to ingested bacterial products may occur, probably linked to the formation of suppressor T lympocytes. However, oral immunization generally leads to increased secretory IgA levels in tears, saliva and nasal secretions[9]. Production of secretory IgA also is essential for the prevention of urinary tract infections[10]. Therefore, oral and systemic immunotherapy currently is viewed as a rational approach for the treatment of mucosa-related infections affecting the respiratory, urinary and intestinal tracts[8].

The active principle of the test drug (uro-vaxom, OM Laboratories, Geneva, Switzerland) used consists of standardized immunostimulatory fractions extracted from E.coli strains. These fractions consists essentially of membrane proteins (glycoliproteins) of high molecular weight and of acidic nature (isoelectric point of approximately 4), which is confirmed by the high content in aspartate and glutamate, and the low content in arginine, lysine and histidine. The concentration in endotoxin is less than 0,1μg/mg active principle. The biochemical standarization of the active principle is based on the glycoliprotein content and the efficacy is controlled routinely by the immunological efficacy models(metabolic activation of macrophages and plague –forming cells

test). The extract is administered orally and activates humoral and cell mediated immune responses. Different immunopathological investigations have shown that it confers protection against experimental infections with E. coli and Pseudomonas aeruginosa, and counteracts antibiotic – induced immunosuppression. Furthermore, it stimulates macrophages, B- lymphocytes, natural killer cells and production of secretory immunoglobulins[10,12]. In man the extract increases the synthesis of serum interferon and urinary secretory IgA as well as the number of active T-lymphocytes[12]. Several clinical trials have demonstrated efficient protection against repeated urinary tract infections[13-18]. AIM: the aim of the study was to asses preventive effects of oral bacterial extracts against acute lower and upper urinary tract infections and to evaluate the effect of this agent on the clinical manifestations, frequency, duration and severity of urinary infections and use of conventional therapy.

Patients - Methods

Initially 30 patients suffering from recurrent urinary tract infection were admitted to the trial. The inclusion criteria were: acute urinary infection with at least 10^5 organisms /ml in midstream urine at initial examination on CLED medium (for total organisms) or Mac Concey medium (for gram negative organisms). The patients had at least 2 recurrences of urinary tract infections during the six month preceding the trial. The exclusion criteria were: dysuria without positive bacteriological findings , indwelling catheter, pregnancy and urinary tract abnormalities. Patients who had been treated with corticosteroids, immunosuppressive or immunostimulant agents were excluding too. Patients were divided into two groups. Each patient in the treated group (group A:20 patients), was given one capsule daily in the fasting state, for 3 consecutive months, contained 6 mg of immunostimulating fractions from e.coli in lyophilized form. The treatment period followed by 6 months observation without treatment. Antibiotics and chemotheraputic agents were given as necessary throughout the trial. In group B (10 patients) we gave only antibiotics and we used them as the control group. The study took place over a period of 9 consecutive months during 2002. The 30 patients who were initially chosen for the trial all completed the 6 months period of follow up. The two groups were comparable regarding pretreatment characteristics.

Table 1 summarizes the general characteristics of the two groups. Clinical examination was performed at the beginning and monthly up the 9 months period and at any possible recurrence of infection. A recurrence was defined as the presence of bacteriuria with $> 10^4$ organisms/ml at any examination after the beginning of the trial.

None of the patients admitted to the hospital. The following laboratory data carried out: full blood count, serum concentrations of creatinine, glucose, urea, IgA, IgM, IgG and urine cultures every month. Antibiotics and chemotherapeutics was allowed for the acute infection , was present at entry and for any eventual recurrence. The concomitant antibiotic or chemotherapeutic agent had to be selected between a broad spectrum of penicillin or cotrimoxazole or nitrofuran. Any other antibiotic could be prescribed only if judged necessary. All concomitant illness and drug therapies were recorded. Side effects, detected by direct observation and indirect questioning , were also recorded and their severity , duration and relation to treatment noted. All 30 patients finished this protocol.

Table 1. *The characteristics of the two groups.*

	Group A	Group B
Patients number	20	10
Female	60%	58%
Mean age	52y (19-76y)	55y (24-72y)
CRF	20%	20%
Nephrolithiasis	20%	20%

Statistical analysis

Statistical comparisons were performed by the student t-test, and the level of significance was set up at $p<0,05$.

Results

The symptom of dysuria present in 95% of the patients at the entry of the study, decreased more markendly in the extract group (12% at 3 months and 6 months) than in control group (21% at 3 and 6 months) ($p=0,05$), approaching the limit of statistical significance.

In the urine culture 80% of the patients revealed gram(-) bacteria (ecoli: 82%, proteus: 7%, klebsiella: 1%). Gram(+) in 20% of the patients(staphylococcus: 4%). The mean value of plasma creatinine was: 2,5mg% in group A and 2,1mg% in group B(NS). We had no statistical differences in the mean values of IgA, IgM, IgG in the serum before and after the bacterial extract . Table 2.

The main clinical evaluation criteria, that is the number of urinary recurrences showed a significant better evolution in the extract than in the control group. The number of recurrences with at least 10^5 bacteria/ml was significantly lower in the extract group during the 9 months of the trial.

Three months after the oral administration of bacterial extract 46% of patients in group A and 55% in group B had one recurrence. After 6 months from the end of receiving the bacterial extract, in group A 37% had one episode and 67% in proup B ($p<0,05$). The intensity and duration of symptoms were diminished in A group in relation with the symptoms in the control group.

Table 2. *Changes in the mean values of immunoglobulins.*

immunoglobulin	group	Before treatment	After 3 months	After 6 months
IgG	A	1165.21	1265.55	1400.80
(800-1800mg%)	B(control)	1140.65	1225.35	1200.35
p		ns	ns	ns
IgA	A	199.55	254.55	260.15
(90-450mg%)	B(control)	240.05	247.14	255.15
p		ns	ns	ns
IgM	A	144.53	174.5	175.14
(60-130mg%)	B(control)	145.5	156.5	160.25
p		ns	ns	ns

Table 3. *Recurences 3 months after the oral bacterial extract.*

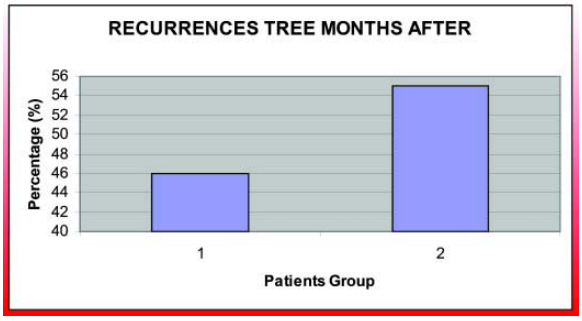
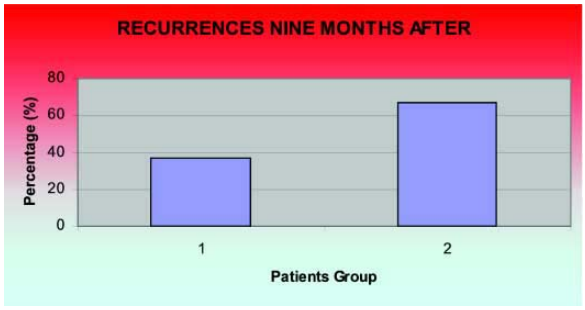


Table 4. *Recurences 6 months after the end of receiving bacterial extracts.*



This decrease in recurrence rate was accompanied by a significant decrease in the consumption of antibiotics and chemotherapeutics (mostly cotrimoxazole and broad spectrum penicillins) which was also more marked during the second half of the study. This antibiotic drug therapy remained the same in 3 and 6 months of observation in the extract group (mean duration 3 days SD:1.1 days) while it increased markedly in the control group. Table 5:

Table 5. *Antibiotic treatment in days*

	extract group	control group	p
initial	5 d (SD:0.5)	5 d (SD:0.8)	NS
3 months	2,7 d (SD:0.9)	3.1 d (SD:1.1)	NS
9 months	3 d (SD:1.1)	9.1 d (SD:2.5)	<0.05

Clinical safety was good, with only 2 side effects reported in the extract group patients. The reported side effects were headache and moderate diarrhoea, no serious enough to discontinue the medicine.

Discussion

The results from this study in 30 patients with acute urinary tract infections have demonstrated the beneficial effect of receiving oral bacterial extracts in management of these infections. The decrease in the number and severity of acute infections in the group with the bacterial extract is in accordance with the results observed by other investigators in series of controlled clinical trials in adults[13-18]. Except the statistically decrease in the number of recurrences in urinary tract infections than placebo does, studies have demonstrated that bacterial extract diminishes the incidence of bacteruria[15,18]. In our study the preventive effect lasted 3 and 6 months after the end of receiving bacterial extract. Shulmann et al 1993 and Popa et al 1996, reported the same effective results[13,14]. However in other clinical trials the beneficial effects of oral administration of these immunostimulants are still relevant 8-12 months after[16,19]. In vitro studies have shown that bacterial extract stimulates the proliferation of lymphocytes[20], stimulates upregulation and downregulation in the metabolic activity of cells[20,21]. Bacterial extract stimulates also the cytokine production , TNF-a [22,23], IL-6[23] and IL-2[22], but we found controversial reports in IL-1 production. It stimulates also the phagocytic activity against S. aureus and candida albicans[23].In vivo trials demonstrated that bacterial extracts stimulate IgG secretion and increase life in infected mice with e-coli, P. aeruginosa[24], it stimulates the production of PFC and anti-SRBC in healthy mice[24] and in immunosupressed mice with antibiotics or mycotoxine[21]. It also stimulates macrophage activity of granulocytes in rabbits[25].

The parameters most frequently chosen to assess efficacy of this medicines are: reduction of the number of infection, reduction in the duration of infection, reduction in the consumption of antibiotics, reduction in absence of work. We focused our observations in the

reduction in the number of infection and in the consumption of antibiotics with quite good results. The duration in antibiotic treatment days diminished significantly especially the second period of our observation except the number of infection recurrences. Effective results in consumption of antibiotics are reported in placebo-control trials to[13,19]. After oral administration, bacterial extract significantly increases the number of T-cells but not the number of B-cells[26]. In the immunoglobulins production we did not notice any significant difference. This may be due to the increased IgA levels in the urinary tract system but not to the systemic blood circulation[11].

Clinical tolerance and safety was good, since reported side effect was minimal with only two side effect reported. In our study this medicine was well tolerated, without serious adverse effects in the examined patients. Other studies refer gastrointestinal disorders and skin reactions but no serious enough to discontinue therapy[26].

In our conclusions patients suffering from recurrent infections in lower and upper urinary tract system may be equipped with a less than normally effective immune response-system. This can be artificially activated by an immunostimulant such this bacterial extract which seems to be safe and effective.

Περίληψη

Μαλλιάρα Μ.* Ανοσοθεραπεία ουρολοιμώξεων με βακτηριακό εκχύλισμα. *Ιπποκράτεια 8 (4):161-165

Σκοπός. Να καταδειχθεί η ασφάλεια και επάρκεια της χρήσης των από του στόματος κεκαθαρμένων βακτηριακών εκχυλισμάτων στην μείωση των υποτροπών των λοιμώξεων του κατώτερου ουροποιητικού.

Ασθενείς και Μέθοδοι. Σε 20 ασθενείς (ομάδα Α) χορηγήσαμε 1 caps βακτηριακού εκχυλίσματος επί 3 συνεχόμενους μήνες με άδειο στομάχι το πρωί ταυτόχρονα με την κατάλληλη αντιβιοτική αγωγή. Όλοι οι ασθενείς είχαν στο ιστορικό τους περισσότερες από 2 ουρολοιμώξεις το τελευταίο εξάμηνο, με συμπτωματολογία δυσουρίας, πυρετού, βακτηριουρίας. Σε άλλους 10 ασθενείς (ομάδα Β) με τα ίδια κριτήρια δεν χορηγήσαμε από του στόματος βακτηριακό εκχύλισμα, αλλά μόνον αντιβιοτική αγωγή και χρησιμοποιήθηκε σαν ομάδα ελέγχου. Η διάρκεια της μελέτης ήταν 9 μήνες. Γυναίκες ήταν σε ποσοστό 60%, χρόνια νεφρική ανεπάρκεια και νεφρολιθίαση εμφάνιζαν σε ποσοστό 20% και στις δύο ομάδες. Λοίμωξη με gram(-) οργανισμούς εμφάνιζαν στο 80%.

Αποτελέσματα. Τρεις μήνες μετά το πέρας της αγωγής με το βακτηριακό εκχύλισμα 54% των ασθενών της ομάδας Α δεν εμφάνισε υποτροπή. 6 μήνες μετά το πέρας της θεραπείας με το βακτηριακό εκχύλισμα 37% των ασθενών της ομάδας Α και 67% της ομάδας Β παρουσίασαν υποτροπή λοίμωξης ($p<0,05$). Η διάρκεια και σοβαρότητα των συμπτωμάτων αναφέρθηκε ελαττωμένη στην ομάδα Α σε σχέση με την ομάδα ελέγχου. Ανεπιθύμητες ενέργειες όπως κεφαλαλγία και διάρροια αναφέρθηκαν σε ποσοστό 4% σε ασθενείς της ομάδας Α, μη ικανές στη σοβαρότητα ώστε να διακοπεί η αγωγή.

Συμπέρασμα. Η χρήση των από του στόματος καθαρμένων βακτηριακών εκχυλισμάτων βοηθά στη μείωση της σοβαρότητας και του αριθμού των υποτροπών σε λοιμώξεις του ουροποιητικού . Τα βακτηριακά εκχυλίσματα φαίνεται πως είναι ασφαλή στην χορήγηση και δεν συνοδεύονται από σοβαρές ανεπιθύμητες ενέργειες.

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