Urinary tract infections and their prevention

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Abstract
Context: This article reviews diverse aspects of the prevention of urinary tract infections, including confirmation of the diagnosis, application of hygiene and dietary measures, antibacterial prophylaxis (preferably consisting of a single nocturnal oral dose per day of an antibiotic or drug with high urinary excretion and good tolerance), and administration of vaccines made with Escherichia coli and other Gram-negative bacilli, consisting of immunostimulating fractions of E. coli strains or E. coli type-1 fimbriae administered through the parenteral or oral route.

Objective: We aimed to review the new preventive measures against urinary tract infections.

Acquisition and synthesis of evidence: We reviewed various microbiological aspects, as well as the physiopathology and virulence factors of uropathogenic E. coli strains expressing type-1 and P fimbriae. The association between blood groups and urinary tract infections in blood group antigen-secretors and nonsecretors was analyzed.

Conclusions: New preventive measures against urinary tract infection consist of the use of phenol-inactivated vaccines administered via the mucosal route, inhibitors of bacterial adherence and biofilm formation, and cyclic adenosine monophosphate stimulators, especially in women aged between puberty and menopause, who show the highest incidence of these infections.

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Prevention of urinary tract infection

Urinary tract infection (UTI) is one of the most common ailments of the human being, from its earliest days until senescence. Its prevalence in both sexes and in the different age groups is variable. In the first 3 months of life, the UTI is more common in males due to structural abnormalities such as the presence of posterior urethral valves. This fact proves that an obstacle that opposes the elimination of urine, causing its retention in any segment of the tract, is a predisposing factor for infection.

From that age, the UTI is more common in females due to a functional cause, the reflux of urine due to vesicoureteral valve incompetence, which is usually corrected spontaneously with puberty. If the infection is not controlled, the responsible bacteria can reach the developing renal pelvis and kidneys intraluminally, resulting in multiple episodes of pyelonephritis that cause renal scarring and, consequently, chronic renal failure.1

In the case of males, the UTI in childhood usually occurs as in the newborn, secondary to the presence of major structural changes in the tract that usually require surgical correction. From about 15 to 50 years of age, the UTI is virtually nonexistent in men, while in women it has a prevalence that may reach 3% of the population. Sexual activity is an important risk factor in these cases.2 In both sexes, from 50 years of age, anatomical modifications (prostatic hypertrophy in men) and physiological modifications (menopause in women) predispose to the UTI, sometimes chronic, and often asymptomatic or tolerated locally and systemically to the point of being considered by some to be a normal consequence of aging that, in most cases, does not require antibacterial treatment.3

It is curious that this scenario of morbidity has not changed in the last 2000 years, and the few achievements in the prevention of the UTI in all ages, particularly young women, also draws attention despite the great medical advances over the past decades. It seems necessary to carry out an approach about the possibility to apply preventive measures, if not to eradicate, at least to significantly reduce the number of annual episodes of cystitis that some of these women suffer with the resulting personal and work disorders. Moreover, in this important population group, the frequency of UTI increases during pregnancy and poses a risk to the mother (pyelonephritis, preeclampsia, eclampsia, hypertension) and fetus (prematurity, low birth weight, perinatal death).

The first and most obvious preventive measure is the confirmation that we have a sick child or adult, man or woman, who has UTI. This is not so easy at times, especially in childhood and old age, when the clinical profile may not be very expressive, with few signs and symptoms that point to the urinary tract as a settlement of the infection.4 But, the introduction of hygiene-dietary measures is possibly the cornerstone of effective prevention.

The main measures of behavior change are:

1. Increase of fluid intake in order to dilute and remove the bacteria that reach the bladder with abundant and frequent urination.
2. Postdefecation anal cleansing in women, always anteroposteriorly, with the intention of not providing fecal flora in the periurethral area.
3. Postcoital douche or, better still, postcoital urination.
4. Correction of constipation in children and adolescents.
5 Intake of cranberry juice.\textsuperscript{6,7} This latter measure is based on the high content of flavonoids (proanthocyanidins) in the cranberry, and their ability to acidify the urine pH. Moreover, being eliminated in the urine, they are attached to the bacterial fimbriae receptors of the urothelial cells of the bladder preventing bacterial adherence.

Acidification of the urine with hippuric acid or vitamin C appears to be another effective preventive measure that aims to achieve a lower urinary pH, which makes the growth of bacteria in the bladder difficult. The downside is that the ingestion of such high amounts of the acidifying agent that, from the practical point of view are unattainable, is needed. Administration of a long-term prophylaxis, for 10 months out of 12, involves a single daily evening dose of antibiotics orally (e.g. fosfomycin trometamol or amoxicillin) or chemotherapy (e.g. cotrimoxazole, nitrofurantoin, nalidixic acid or norfloxacain) with high urinary excretion. The main drawbacks of this preventive measure are the induction of bacterial resistance, the phenomenon of intolerance and drug toxicity and the modification of the fecal and vaginal flora, derived from its long administration.\textsuperscript{8}

The increase of antimicrobial resistance of microorganisms causing UTI, especially \textit{Escherichia coli}, is stimulating interest for preventive methods other than the classical chemoprophylaxis. Recently, several vaccine preparations have been developed, mainly a whole-cell parenteral vaccine (Solco Urovac\textsuperscript{6}), an oral vaccine (Uro-Vaxom\textsuperscript{8}) consisting of immunostimulating fractions of 18 serotypes of \textit{E. coli} and two parenteral vaccines of fimbriae of \textit{E. coli} type 1.

The main aim for the control of the UTI is the knowledge of the different, both therapeutic and diagnostic, alternatives and their prevention in all populations, mainly in the age groups at highest risk for this condition, represented by women between the puberty and menopause, and within them, the infections that occur during pregnancy, not only the typical cystitis, but the most important gravid pyelonephritis. We reviewed the available evidence regarding the new measures for the prevention of the UTI.

New preventive measures for the urinary tract infection

Microbiology and virulence factors

The organism most often involved in the pathogenesis of the urinary tract infections is \textit{E. coli}, which is estimated as the first agent involved in more than 90\% of cases. Of the more than 170 serotypes of \textit{E. coli} capable of inducing UTI, only 6 are responsible for more than 80\% of the episodes of acute pyelonephritis, and this high frequency is explained by the large number of members of the species that make up the normal flora of the large intestine and develop the infection due to contamination from the urethra, especially in women who are anatomically predisposed by the shortness of it. Orskov et al.\textsuperscript{9} and Johnson et al.\textsuperscript{10} pointed out that the most frequently responsible serotypes of \textit{E. coli} serve the following antigens: O1, O2, O4, O6, O7, O16, O18, and O75 (somatic), and K1, K2, K5, K12, and K13 (capsular).

Nowadays, the presence or absence of fimbriae/adesins and the type they belong to is considered the crucial factor of the early development of the UTI, and it deserves special attention. They are common in most gram-negative bacteria, and especially in \textit{E. coli}, type 1 or mannose sensitive (MS) and Type P or mannose resistant (MR) fimbriae, which are characterized by the ability to agglutinate red blood cells in the presence or absence of mannose, are the most studied. Type 1 fimbriae are usually associated with lower urinary tract infections (cystitis) and type P fimbriae with upper urinary tract infections (pyelonephritis). \textit{E. coli} can contain several types of fimbriae and also experience the phenomenon known as ‘phase variation’, which is manifested by a change in the expression of the fimbriae.

The usual route of the urinary tract infection is ascending, even when the anterior urethra is colonized by microorganisms without pathogenic significance. In the case of women, because of their anatomical features, this approach takes on added importance. Among the factors that predispose it, voiding with incomplete bladder emptying is the most important functional cause, along with decreased urinary flow and manipulation by catheters; prostatic hypertrophy, increased vaginal pH, and anatomical and functional changes of the bladder are also involved.

Recurrent infections are classified, according to their pathogenesis, in relapses and reinfections. These are due to new infections caused by the same strain or a different one, and in the case of young women, they occur in more than 20\% of those who have suffered a first episode of cystitis. It has been shown that these women more often have, when compared with women without UTI, the non-secretor serotype of blood groups and, in the membranes of their epithelial cells, they express only two globo- sialy gal-globoside (SGG) and disialosyl gal-globoside (DSGG), which are not expressed by secretory women that act as receptors of uropathogenic \textit{E. coli}.

Recently, in experimental animals, it has also been observed that uropathogenic bacteria invade the superficial cells of the bladder and that biofilms\textsuperscript{12} are created within them that may be a reservoir for microorganisms producing recurrent urinary tract infections. In any case, the first step for the infection to occur involves microbial attachment to uroepithelial cells, carried out by bacterial adhesion structures called fimbriae.\textsuperscript{13}

Autovaccines and suspensions of fimbriate \textit{E. coli}

The urinary tract infection is a serious problem, both from a social and a medical point of view. To the trouble of the medical profile, we must add absenteeism from work, drug costs, and the induction of antimicrobial resistance. Besides, there are well-known risk populations and resulting from medical interventions in urological surgery, bladder catheterization, and spinal injuries in which the clinical practice is antimicrobial prophylaxis.\textsuperscript{14-16} Another special situation is pregnancy associated with asymptomatic bacteruria, in which 20–40\% of these cases develop pyelonephritis\textsuperscript{17} that generate renal damage and fetal problems including intrauterine growth retardation, prematurity, risk of perinatal death, and congenital anomalies.\textsuperscript{18}
A separate section is the relation between blood groups and the UTI. The blood group antigens A, B, and O are related with the adherence through the fimbriae of microorganisms such as *E. coli* to the cells of the uroepithelium and, in particular, the individuals of groups A and O, which have antibodies against B antigen, show greater resistance to the urinary tract infection than those who do not have the mentioned antibodies (groups B or AB). Another important predisposing factor lies in the characterization of the subjects as secretor or non-secretor. Secretors are those who have their blood group antigens in the red blood cells and other body fluids such as saliva and mucus, where they can also be ascertained. On the other hand, non-secretors are those who present their blood group antigens in red blood cells only. In the general population, it is estimated that 80% are secretors and 20% are non-secretors. It has been ascertained that, for example, individuals of type B blood group and non-secretors have an increased predisposition to UTI.

The need to know the risk groups by their frequency and severity requires new approaches for prevention and treatment of the UTI. The use of activators of the immune system as inactivated bacterial whole-cell vaccines or lysates of them has been recently evaluated, incorporating different routes of immunization.

The phenomenon of adherence in gram-negative bacilli, which is performed through the fimbriae in whose distal ends are adhesins, has been recently involved with the process of biofilm formation. Communities of microorganisms irreversibly attached to a surface that cause recurrence or chronicity of over 80% of chronic infections caused by bacteria, among which the UTIs are included, have been identified. For the genesis of vaccines, the selection of *E. coli* strains isolated from urine cultures of patients, inactivated with methods that preserve antigenicity to the full, and correctly categorized and identified as internationally accredited producing type 1 fimbriae and P fimbriated *E. coli* strains is transcendent. The basis of this therapy involves the induction of antibodies during active immunization that would lead to increased resistance to colonization in genital and urinary tract areas, and activate immunocompetent cells that increase antibody production and prevent the invasion of tissues.

The use of inactivated bacteria ensures the presence of most of the potential virulence factors with potential protection, but their safety must also be considered, for example, through detoxification, given the presence of endotoxins of gram-negative bacilli. The local route of local administration or mucosa might be more effective than the parenteral one in terms of local antibody induction.

**Inhibitors of bacterial adherence**

The main inhibitors of bacterial adherence described to the present are naturally occurring polyphenols, and they constitute a series of metabolites of the plants synthesized by them from a phenylalanine molecule and three molecules of malonyl-coenzyme A.

It is interesting to emphasize the antibacterial properties of the flavonoid group included in the condensed tannins or proanthocyanidins. Proanthocyanidins, specifically those of type A, are the active ingredients responsible for the inhibitory activity of the adherence of bacteria such as *E. coli* to the epithelial cells of the urinary tract, and they are the substance responsible for the activity present in the American cranberry *Vaccinium macrocarpon*.

Other adherence inhibitor compounds are catechins, a type of proanthocyanidins or condensed tannins. They are oligomers and polymers of flavan-3-ol, which are widely distributed in the plant kingdom. The most abundant flavan-3-ol units in nature are (+)-catelein, (+)-gallocatein, and their diastereomers (−)-epicatelein, (−)-epicatechin, and (−)-epigallocatechin. The proanthocyanidins exclusively constituted of (epi)catechin are called procyanidins. Type A procyanidins have an ether bond between the C-2 carbon of the upper unit (cycle) and the hydroxyl group of the C-7 carbon of the lower unit (cycle) of the three cycles that constitute their structure, while type B ones, which lack that bond, are found in many plant species. There are few natural sources in which type A proanthocyanidins have been identified (blueberry, peanut, avocado, plum, cinnamon and curry), which are those that act as inhibitors of bacterial adherence to cell and bacterial biofilm formation receptors.

**Inhibitors of bacterial biofilms**

In fact, bacterial biofilm formation is a major cause of chronic infections and antibiotic treatment failure thereof. The biofilm prevents access of antimicrobial agents, and even of antibodies, so, if its formation is not obstructed or its rupture occurs once formed, the infection is perpetuated. Several substances are known to inhibit its development, among which are type A proanthocyanidins, hesperidin, apigenin, naringin and rhoifolin, among others.

Biofilms are clusters of cells (bacteria) usually in mixed populations (communities) that attach to a surface and form a structure in three dimensions, linked by extracellular polymeric substances (matrix polysaccharides) produced by themselves and composed of organic and inorganic elements. They are the usual state of bacteria in nature. They present phenotypic characteristics different from their planktonic or free equivalents, and they are highly resistant to antibiotics and disinfectants. The production of biofilms is involved in over 60% of chronic infections. To give some examples, the presence of biofilms in organic tissues and inert surfaces has been shown, in conditions as varied as endocarditis in native heart valves, osteomyelitis, and many musculoskeletal infections, tonsillitis, oitis media, sinusitis, periodontitis, and in the infection associated with all types of prostheses, cannulas and catheters.

**Stimulators of cyclic adenosine monophosphate: forskolin**

The efficacy of forskolin in the treatment of the UTI has been proven by increasing the content of cyclcal adenosine monophosphate (AMP) in urothelial cells, leading uropathogenic bacteria to go out of it. Once in the epithelial cell, the microorganisms are able to resist antibiotic treatment, constituting an intracellular reservoir by binding to Rab 27 b/CD 63 positive vesicles.
Cyclic AMP levels regulate the exocytosis of these vesicles depending on the bladder distension. Forskolin, which is the active component of the Coleus forskohlii plant, of the labiatae family, is able to increase those levels in the epithelial cells. This would favor the exocytosis of the uroplakin vesicles and would release the uropathogenic bacteria of the intracellular reservoir to the light. These considerations could lead to open new paths for the treatment of recurrent urinary tract infections.23

Conclusion

Although there is little scientific evidence for this, new ways are being developed aimed at the prevention of the urinary tract infection. Some of these measures are widely distributed with variable efficacy. Among them are the increase of the intake and liquid discharge, anteroposterior anal postdefecation cleansing, postcoital urination, correction of constipation, and prolonged antibacterial prophylaxis with antibiotics or well tolerated and of high urinary excretion chemotherapeutic agents. Moreover, there are new expectations with the use of inhibitors of bacterial adherence to urothelial cell and inhibitors of biofilm formation receptors. The development of new measures such as stimulators of cyclic AMP inside urothelial cells, or the development of vaccines composed of whole bacteria, fimbriated bacteria elaborated from infecting microorganisms themselves (autovaccines) or with subcellular components (fimbriae/adhesins) are an interesting initiative in this field.

Conflict of interest

Drs. F. González-Chamorro and D. Dámaso have no conflict of interest.

Drs. R. Palacios and J. Campos work for the Diater laboratory.

Dr. F. Borrego works for the Zoster company of the Ferrer Group.

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